Recent epidemiologic, genetic, and molecular studies suggest infection and inflammation initiate certain cancers, including those of the prostate. The American Cancer Society, estimates that approximately 20% of all worldwide cancers are caused by infection. Mycoplasma, a genus of bacteria that lack a cell wall, are among the few prokaryotes that can grow in close relationship with mammalian cells, often without any apparent pathology, for extended periods of time. In this study, the capacity of Mycoplasma genitalium, a prevalent sexually transmitted infection, and Mycoplasma hyorhinis, a mycoplasma found at unusually high frequency among patients with AIDS, to induce a malignant phenotype in benign human prostate cells (BPH-1) was evaluated using a series of in vitro and in vivo assays. After 19 weeks of culture, infected BPH-1 cells achieved anchorage-independent growth and increased migration and invasion. Malignant transformation of infected BPH-1 cells was confirmed by the formation of xenograft tumors in athymic mice. Associated with these changes was an increase in karyotypic entropy, evident by the accumulation of chromosomal aberrations and polysomy. This is the first report describing the capacity of M. genitalium or M. hyorhinis infection to lead to the malignant transformation of benign human epithelial cells and may serve as a model to further study the relationship between prostatitis and prostatic carcinogenesis.

AIM: To explore relationships between human carcinomas and mycoplasma infection. .... RESULTS: Fifty of 90 cases (56%) of gastric carcinoma were positive for mycoplasma hyorhinis. In other gastric diseases, the mycoplasma infection ratio was 28% (18/64) in chronic superficial gastritis, 30% (14/46) in gastric ulcer and 37% (18/49) in intestinal metaplasia. The difference is significant with gastric cancer (chi(2) = 12.06, P < 0.05). In colon carcinoma, the mycoplasma infection ratio was 55.1% (32/58), but it was 20.9% (10/49) in adenomorous polyp (chi(2) = 13.46, P < 0.005). Gastric and colon cancers with high differentiation had a higher mycoplasma infection ratio than those with low differentiation (P < 0.05).
Mycoplasma infection in esophageal cancer, lung cancer, breast cancer and glioma was 50.9% (27/53), 52.6% (31/59), 39.7% (25/63) and 41% (38/91), respectively. The mycoplasma DNA was successfully amplified with the DNA extracted from the cancer tissues that were positive for mycoplasma infection (detected with antibody PD4). CONCLUSION: There was high correlation between mycoplasma infection and different cancers, which suggests the possibility of an association between the two. The mechanism involved in oncogenesis by mycoplasma remains unknown.

TITLE: Mycoplasma infection in human gastrointestinal carcinoma tissues

Zhonghua Yi Xue Za Zhi. 2001; 81(10):601-4 (ISSN: 0376-2491) Huang S; Shou C; Wu J
BeiJing Institute for Cancer Research, Peking University School of Oncology, 100034, China.

OBJECTIVE: To explore the association between the carcinoma and mycoplasma infection by immunohistochemistry. ....... RESULTS: It was showed that mycoplasma was present in 56% (50/90 cases) of gastric carcinoma. The cancer tissues with high differentiation had a higher mycoplasma infection ratio than that of low differentiation cancer tissues. (P < 0.05). In control cases, mycoplasma infection was 28% (18/49) in chronic superficial gastritis, 30% (14/46) in gastric ulcer and 37% (18/49) in intestinal metaplasia of the stomach. Mycoplasma infection was 55.1% (32/58) in colon carcinoma and 20.9% (10/49) in adenomorous polyp (P < 0.005). It seems that colon carcinoma tissues with slight pathological grade had a higher percent of mycoplasma infection than that of cancer tissues with moderate and heavy pathological grade (P < 0.05). CONCLUSION: The high infection of mycoplasmas in carcinoma tissues suggest an association between mycoplasma and cancer. The mechanism involved in oncogenesis by mycoplasmas remains to be elucidated.


Our previous studies show that some mycoplasmas are able to induce malignant transformation of host mammalian cells. This malignant transformation is a multistage process with the early infection, reversible and irreversible stages, and similar to human tumor development in nature...A prolonged infection by mycoplasmas lead to the expression of more cancer related genes at the irreversible stage. CONCLUSION: The results indicate that the expression profiles correspond with the phenotypic features of the cells in the mycoplasma induced transformation process. The early mycoplasma infection stage shares a common phenomenon with many other acute infections, genes with increased expression significantly outnumbering those with decreased expression. The reversible stage is a transition stage between benignancy and malignancy at the molecular level. Aberrant expression of oncogenes and tumor repressors plays a key role in mycoplasma-induced malignant transformation

TITLE: p37 Induces tumor invasiveness. AUTHORS: Ketcham CM, Anai S, Reutzel R, Sheng S, Schuster SM, Brenes RB, Agbandje-McKenna M, McKenna R, Rosser CJ, Boehlein SK. SOURCE: Mol Cancer Ther. 2005 Jul;4(7):1031-8. Department of Biochemistry and Molecular Biology, College of Medicine, University of Florida, Gainesville, 32610, USA. Previous studies have shown a statistically significant correlation between human carcinomas and monoclonal antibody detection of a Mycoplasma hyorhinis-encoded protein known as p37. These observations suggest that M. hyorhinis can infect humans and may facilitate tumor invasiveness via p37. These results further suggest that p37 may be a molecular target for cancer therapy.


OBJECTIVES: To investigate the association between Mycoplasma sp. infection and conventional renal cell carcinoma (RCC). CONCLUSIONS: The relationship between mycoplasma infection and conventional RCC has been investigated for the first time, and a significantly high existence of Mycoplasma sp. DNA was found in the tissues of patients with conventional RCC compared with that found in a healthy control group. This suggests that mycoplasma-mediated multistage carcinogenesis may play a role in the development of RCC.

TITLE: An association of disseminated Mycoplasma fermentans in HIV-1 positive patients with non-Hodgkin's lymphoma. AUTHORS: Ainsworth JG, Easterbrook PJ, Clarke J, Gilroy CB, Taylor-Robinson D. SOURCE: Int J STD AIDS. 2001 Aug;12(8):499-504. Genitourinary Medicine Section, Division of Medicine, Imperial College School of Medicine, St Mary's Hospital, London, UK. We examined the relationship between the haematogenous dissemination of Mycoplasma fermentans and non-Hodgkin's lymphoma (NHL) in 265 HIV-1 positive patients.... We found a statistically significant association between the presence of M. fermentans and the development of NHL in the combined cohort.


TITLE: Mycoplasma infection and cancer. AUTHORS: Ning JY, Shou CC. Department of Biochemistry and Molecular Biology, Beijing Institute for Cancer Research, School of Oncology, Peking University, Beijing, 100034, PR China.
Mycoplasma infection can be detected in many tumor tissues, continuous infection of mycoplasma can lead to transformation of mammalian cells, up-regulating expression of oncogenes, and some biologic changes of tumor cells, suggesting association of mycoplasma infection with tumorigenesis.

**TITLE:** Mycoplasma infections and different human carcinomas. **AUTHORS:** Huang S, Li JY, Wu J, Meng L, Shou CC. Department of Biochemistry and Molecular Biology, Beijing Institute for Cancer Research and Peking University School of Oncology, No.1 Da Hong Luo Chang Street, Western District, Beijing 100034, China. 6201@us.sina.com. **SOURCE:** World J Gastroenterol. 2001 Apr;7(2):266-9.

**AIM:** To explore relationships between human carcinomas and mycoplasma infection. **CONCLUSION:** There was high correlation between mycoplasma infection and different cancers, which suggests the possibility of an association between the two. The mechanism involved in oncogenesis by mycoplasma remains unknown.


**OBJECTIVE:** To explore the association between the carcinoma and mycoplasma infection by immunohistochemistry. **CONCLUSION:** The high infection of mycoplasmas in carcinoma tissues suggest an association between mycoplasma and cancer. The mechanism involved in oncogenesis by mycoplasmas remains to be elucidated.


**OBJECTIVE:** To determine the prevalence of Mycoplasma hyorhinis in archived paraffin-embedded gastric cancer tissue and to find whether Mycoplasma hyorhinis infection can influence gene expression level in gastric cancer cells. **METHODS:** A high-dense tissue microarray containing 105 gastric cancer samples, 101 benign margin samples and 62 non-cancerous gastric disease samples resected during operation was constructed. PD4, a specific anti-Mycoplasma-hyorhinis Mab, was used to detect the infection rate in all the samples in the tissue microarrays immunohistochemically. Then, cDNA microarray was used to pinpoint differentially the expressed genes between gastric cancer cell line MGC803 samples with and without Mycoplasma hyorhinis infection. **RESULTS:** The infection rate of M. hyorhinis was 54.1% 53/98 in gastric cancer samples, 51.7% 45/87 in benign margin samples, and 15.8 % 9/57 in non-cancerous disease samples respectively. The difference of infection rates between gastric cancer and non-cancerous gastric disease was statistically significant (p = 0.001). Highly differentiated adenocarcinomas had more opportunity (84.6%) to be infected with
M. hyorhinis than poorly differentiated ones (45.9%) (P < 0.05). Intestinal type of gastric cancers (according to Lauren's classification) got the infection more often than diffused type. About 409 gene expression alterations were detected in 48,000 sites from two gastric cancer cell lines and the expression levels of some genes correlating with cell apoptosis and cell adhesion were down regulated after Mycoplasma hyorhinis infection. CONCLUSION: The infection rate of M. hyorhinis is significantly higher in gastric cancer than in other gastric diseases, thus indicating the association between Mycoplasma infection and gastric cancer. Mycoplasma hyorhinis infection influences the gene expression level in gastric cancer cell line MGC803, which indicates that the infection could have something to do with the process of gastric cancer. The question whether M.hyorhinis has oncogenic potential remains to be elucidated.


We examined the relationship between the haematogenous dissemination of Mycoplasma fermentans and non-Hodgkin's lymphoma (NHL) in 265 HIV-1 positive patients. A polymerase chain reaction (PCR) assay was used to detect M. fermentans in peripheral blood mononuclear cells (PBMCs) from 50 patients enrolled consecutively from an HIV outpatient clinic in 1991 (cohort 1), 56 patients with lower respiratory tract infection who underwent bronchoscopy in 1992 (cohort 2), and 159 patients who were enrolled into a natural history cohort study in 1994 (cohort 3). The incidence of NHL among the patients was determined in 1998. The PBMCs of 29 patients (10.9%) were positive for M. fermentans (8 in cohort 1, 13 in cohort 2 and 8 in cohort 3) and 11 patients (4.2%) developed NHL which was confirmed histologically (3 in cohort 1, 4 in cohort 2 and 4 in cohort 3). We found a statistically significant association between the presence of M. fermentans and the development of NHL in the combined cohort (risk ratio [RR]=6.78 [95% confidence interval (CI) 2.21--20.84], P=0.003 Fisher's exact test [FET]). This association remained significant even after adjustment in a multivariate analysis for CD4 cell count and HIV disease status at the time of M. fermentans testing.

TITLE: Induction of leukemia cell differentiation and apoptosis by recombinant P48, a modulin derived from Mycoplasma fermentans. AUTHORS: Hall RE, Agarwal S, Kestler DP. SOURCE: Biochem Biophys Res Commun. 2000 Mar 5;269(1):284-9. Department of Medicine, University of Tennessee Medical Center/Graduate School of Medicine, Knoxville, Tennessee 37920, USA. rhall@utkux.utcc.utk.edu

P48 is a 48-kDa monocytic differentiation/activation factor which was originally identified in the conditioned medium of the Reh and other leukemia cell lines and has recently been shown to be a Mycoplasma fermentans gene product. Previously, conditioned medium P48 has been shown to induce differentiation of HL-60
(human promyelocytic leukemia) cells. Recently our laboratory isolated cDNA clones for P48 from Reh cells and genomic clones from Mycoplasma fermentans and expressed the recombinant protein as a maltose binding protein (MBP) fusion protein in E. coli. In this report we present the initial characterization of this recombinant P48 fusion protein (rP48-MBP). We show that rP48-MBP induces differentiation of HL-60, U937 (human histiocytic lymphoma), and M1 (mouse myeloid leukemia) cell lines. Interestingly, rP48-MBP also induces apoptosis of U937 and HL-60 cells as assessed by terminal transferase (TUNEL) assays. This is the first report of induction of apoptosis by a Mycoplasma gene product. P48 is a Mycoplasma-derived immunomodulatory molecule which has differentiation and apoptosis-inducing activities and may be important in the pathophysiology of Mycoplasma infections. The recombinant protein may be useful in studying the mechanisms of differentiation, cytokine production, and apoptosis in malignant and nonmalignant hematopoietic cells. Copyright 2000 Academic Press.


To better understand how infections by mycoplasmas affect gene expression in human cells, we quantitatively measured the transcripts of 38 cytokine genes in HPV E6- and E7-immortalized cervical and prostatic epithelial cells before and after infection by four human urogenital mycoplasmas, M. fermentans, M. genitalium, M. hominis and M. penetrans. Using the multi-probe RNase protection assay (RPA), 22 and 23 cytokine gene transcripts were detected in the non-infected control prostatic and cervical epithelial cells, respectively. Although there were no discernible changes in cell morphology and growth kinetics following 72 h of mycoplasmal infection, 55-74% of the cytokine genes expressed in the two human epithelial cell lines were altered. Most changes reflected an increased expression of these cytokine genes, while expression of some cytokine genes significantly decreased. The effects varied with host cell type and species of infecting mycoplasmas. These alterations in gene expression were more profound in the cervical epithelial cells than in the prostatic cells. M. fermentans produced the most significant effects, followed by M. penetrans, M. genitalium and M. hominis. Some alterations in the gene expression were transient, but most persisted over the course of chronic (9 months) mycoplasmal infection. Prolonged gene expression changes induced by chronic mycoplasmal infection may gradually alter important biological properties in the infected mammalian cells and produce a unique form of disease process.


Chronic persistent infections by mycoplasmas induced malignant transformation of C3H mouse embryo cells that normally had never been reported to undergo
spontaneous transformation. This mycoplasma-mediated oncogenic process had a long latency (more than 7 weeks of continuous mycoplasmal infection) and showed a multistage progression characterized by reversibility (at least up to 11 weeks of mycoplasmal infection) and irreversibility of malignant properties upon removal of the mycoplasma from culture. Further prolonged infections (18 weeks) by Mycoplasma fermentans or M. penetrans resulted in permanent transformation of these C3H cells that no longer required the continued presence of the transformation-inducing mycoplasmas in cultures to retain their malignant properties. Previous studies of viral oncogenesis revealed that virus-transformed cells always had viral gene(s) present. Integration of viral gene(s) apparently played an important role in the process of oncogenesis. In this study, we examined if the continued presence of any mycoplasmal gene(s) in mammalian cells, in whatever form, was also crucial in causing malignant cell transformation. Representational difference analysis (RDA) was a recently developed powerful technique to compare differences between two complex genomes. In the RDA system, subtractive and kinetic enrichment was used to purify and isolate restriction endonuclease gene fragment(s) of mycoplasmal origin, presumably present only in mycoplasma-transformed C3H cells, but not in nonmycoplasma-exposed control C3H cells. After three rounds of subtractive hybridization following PCR enrichment for each of three different restriction enzymes DNA digests, no gene fragment of mycoplasmal origin was amplified or identified in the permanently transformed C3H cells. Differing from tumorigenesis in animal cells induced by most oncogenic viruses or in plant cells induced by Agrobacteria, mycoplasmas evidently did not cause malignant transformation by integrating their gene(s) into the mammalian cell genome.

PRE-2000 ARTICLES ARCHIVE


ABSTRACT: Oncogenic potential of human mycoplasmas was studied using
cultured mouse embryo cells, C3H/10T1/2 (C3H). Mycoplasma fermentans and Mycoplasma penetrans, mycoplasmas found in unusually high frequencies among patients with AIDS, were examined. Instead of acute transformation, a multistage process in promotion and progression of malignant cell transformation with long latency was noted; after 6 passages (1 wk per passage) of persistent infection with M. fermentans, C3H cells exhibited phenotypic changes with malignant characteristics that became progressively more prominent with further prolonged infection.

Up to at least the 11th passage, all malignant changes were reversible if mycoplasmas were eradicated by antibiotic treatment. Further persistent infection with the mycoplasmas until 18 passages resulted in an irreversible form of transformation that included the ability to form tumors in animals and high soft agar cloning efficiency. Whereas chromosomal loss and translocational changes in C3H cells infected by either mycoplasma during the reversible stage were not prominent, the onset of the irreversible phase of transformation coincided with such karyotypic alteration. Genetic instability--i.e., prominent chromosomal alteration of permanently transformed cells--was most likely caused by mutation of a gene(s) responsible for fidelity of DNA replication or repair. Once induced, chromosomal alterations continued to accumulate both in cultured cells and in animals without the continued presence of the transforming microbes. Mycoplasma-mediated multistage oncogenesis exhibited here shares many characteristics found in the development of human cancer.


ABSTRACT: C3H mouse embryo cells, which normally have low inherent spontaneous transformation, underwent malignant transformation while chronically infected with Mycoplasma fermentans or Mycoplasma penetrans. This mycoplasma-mediated oncogenic process had long latency (more than 7 weeks of persistent mycoplasmal infection) and showed multistage progression characterized by reversibility and irreversibility of malignant properties upon removal of M. fermentans from culture. Marked expression of H-ras and c-myc mRNA, but not N-myc, src, N-ras, or p53 mRNA, was found in the mycoplasma-transformed C3H cells that exhibited characteristic malignant properties of morphological changes and uncontrolled cell growth.

However, at least up to the eleventh week of persistent mycoplasma infection, the marked expression of H-ras or c-myc mRNA in C3H cells depended on continued presence of the mycoplasma in culture. H-ras or c-myc mRNA rapidly declined to the undetectable low levels of nontransformed parental C3H cells, and all malignant properties of the once-fully-transformed C3H cells quickly reversed, if M. fermentans was eradicated from culture. In comparison, infection with M. penetrans for 7 or 11 weeks also induced a high level of H-ras, but not c-myc, mRNA expression in C3H cells. Despite having prominent amount of steady-state H-ras mRNA, these M. penetrans-infected C3H cells did not show any sign of malignant transformation.
Thus, marked expression of H-ras gene alone was not sufficient to effect transformation in C3H cells. Interestingly, after a further prolonged (18 weeks) infection with either M. fermentans or M. penetrans, C3H cells revealed prominent chromosomal changes, expressed constitutively (with or without the presence of the transforming mycoplasmas) at high levels of both H-ras and c-myc mRNA and became permanently transformed. These cells were able to form tumors in animals.


Abstract: Mycoplasmas are tiny polymorphic prokaryotic organisms (0.2-0.3 microm) that lack a cell wall and reside ubiquitously at the cell membrane or internalized into the cell. The organisms have been implicated in many diseases including functioning as cofactors catalyzing the HIV disease state. The oncogenic potential of mycoplasmas was only recently realized when they were shown to cause chromosomal changes and in vitro cell transformations through gradual progressive chromosomal loss and translocations. While a recent study linked mycoplasmas with gastric cancer, the association between mycoplasmas and ovarian cancer has not been established. Recently, a commercial assay which combined polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA) methods was developed for the detection of mycoplasmas. The present objective was to determine the prevalence of mycoplasmas in archived paraffin-embedded malignant ovarian cancer tissue. The combined PCR-ELISA procedure was used with consensus primers targeting for 15 species of mycoplasmas and acholeplasmas. Archived human malignant ovarian cancer tissues (N = 27 cases) embedded in paraffin blocks were processed, and DNA was extracted and the presence of DNA verified. The extracted DNA specimens were randomly divided into three groups for analyses. PCR-ELISA assays were performed on extracted DNA together with appropriate negative and positive controls.

The results showed mycoplasmas were present in 59.3% of the malignant ovarian cancer specimens. PCR-ELISA analysis of Neisseria gonorrhoea and Chlamydia trachomatis controls did not produce cross-reacting false-positive results. The results suggest an association between mycoplasmas and malignant ovarian cancer. A 59.3% prevalence rate was demonstrated for mycoplasmas in paraffin-embedded ovarian cancer tissues. The mechanism involved in oncogenesis by mycoplasmas remains to be elucidated.

TITLE: Absence of mycoplasmal gene in malignant mammalian cells transformed by chronic persistent infection of mycoplasmas.

ABSTRACT: Chronic persistent infections by mycoplasmas induced malignant transformation of C3H mouse embryo cells that normally had never been reported to undergo spontaneous transformation. This mycoplasma-mediated oncogenic process had a long latency (more than 7 weeks of continuous mycoplasmal infection) and showed a multistage progression characterized by reversibility (at least up to 11 weeks of mycoplasmal infection) and irreversibility of malignant properties upon removal of the mycoplasma from culture. Further prolonged infections (18 weeks) by Mycoplasma fermentans or M. penetrans resulted in permanent transformation of these C3H cells that no longer required the continued presence of the transformation-inducing mycoplasmas in cultures to retain their malignant properties. Previous studies of viral oncogenesis revealed that virus-transformed cells always had viral gene(s) present.

Integration of viral gene(s) apparently played an important role in the process of oncogenesis. In this study, we examined if the continued presence of any mycoplasmal gene(s) in mammalian cells, in whatever form, was also crucial in causing malignant cell transformation. Representational difference analysis (RDA) was a recently developed powerful technique to compare differences between two complex genomes. In the RDA system, subtractive and kinetic enrichment was used to purify and isolate restriction endonuclease gene fragment(s) of mycoplasmal origin, presumably present only in mycoplasma-transformed C3H cells, but not in nonmycoplasma-exposed control C3H cells. After three rounds of subtractive hybridization following PCR enrichment for each of three different restriction enzymes DNA digests, no gene fragment of mycoplasmal origin was amplified or identified in the permanently transformed C3H cells. Differing from tumorigenesis in animal cells induced by most oncogenic viruses or in plant cells induced by Agrobacteria, mycoplasmas evidently did not cause malignant transformation by integrating their gene(s) into the mammalian cell genome.

TITLE: Metastasis-promoting activity of a novel molecule, Ag 243-5, derived from mycoplasma, and the complete nucleotide sequence. Authors: Ushio S, Iwaki K, et al.


ABSTRACT: We found that mycoplasma-infected cells have a higher ability to metastasize in vivo than non-mycoplasma-infected cells. To investigate this phenomenon, we obtained a monoclonal antibody, MAb 243-5, by immunization with Mycoplasma arginini-infected RPMI 4788 cells. This MAb recognized a mycoplasmal protein with an MW of 47 kDa and completely inhibited the experimental metastasis of M. arginini-infected RPMI 4788 cells using a nude mouse model. Using this MAb, we purified a molecule called Ag 243-5 and determined the N-terminal amino acid sequence and clarified the entire nucleotide sequence of the Ag 243-5 gene. PCR analysis showed the existence of a homologous gene in Mycoplasma hyorhinis. Four sequential injections of Ag 243-5 (30 micrograms/shot) promoted the experimental metastasis of non-mycoplasma-infected RPMI 4788 cells more than 10-fold using a nude mouse model. Ag 243-5 also promoted the experimental metastasis of the non-mycoplasma-infected mouse
colon cancer cell line colon 26. This metastasis-promoting effect was neutralized by MAb 243-5. UI: 96163149

Authors: Ilantzis C, Thomson DM, et al.


Human cancers express organ-specific neoantigens (OSNs) which elicit specific cellular immune responses in the cancer patient, as demonstrated by leukocyte adherence inhibition (LAI), an in vitro immune response assay. A purified protein of MW 40,000 (p40) exhibiting OSN (colon specific) activity was cleaved into specific peptide fragments and their partial amino acid sequences determined. This information was used in the polymerase chain reaction (PCR) to obtain a 992 bpCDNA clone (PCR-992) from a human colon adenocarcinoma cell line (LS-180). By comparison of the predicted amino acid sequence of PCR-992 with the known sequence of p40 peptides, PCR-992 was shown to correspond to almost the entire coding region of p40. Nucleotide sequence analysis suggested that the protein was mycoplasmal in origin due to its high A+T content (76%) and the presence of five in frame TGA termination codons; at least two of the latter are actually read as tryptophan, a known feature of mycoplasma translation. We have confirmed this origin by direct isolation of a contaminating mycoplasma species from the LS-180 cell line and demonstration that it could be hybridized with the PCR-992 probe. Northern and PCR analysis of RNA preparations from the contaminated LS-180 cell line showed that p40 was part of the high affinity transport system operon of Mycoplasma hyorhinis (Dudler et al, EMBO J., 7: 3963-3970, 1988).

Total protein lysates of Mycoplasma hyorhinis cultivated without animal cells could elicit positive LAI responses when incubated with cancer patient leukocytes but not with normal patient leukocytes. The organ-specific nature of the response was, however, not observed indicating that host cell-mycoplasmal interactions may play a role in determining the organ-specific nature of p40 seen with the LAI. The significance of these findings will be discussed in the context of previous thinking regarding the origin of OSNs. UI: 93275244

TITLE: A mycoplasma high-affinity transport system and the in vitro invasiveness of mouse sarcoma cells. Authors: Dudler R, Schmidhauser C

SOURCE: EMBO J 1988 Dec 1;7(12):3963-70

ABSTRACT: FS9 mouse sarcoma cells were previously shown to be highly invasive when confronted with chicken heart fibroblasts using Abercrombie’s confronted explant technique. This invasion could be inhibited by addition to the assay of Fab fragments of a monoclonal antibody directed against p37, a protein associated with the surface of FS9 cells. We have cloned and sequenced the gene for p37. We show that it originates from Mycoplasma hyorhinis and that UGA is a
tryptophan codon in this organism. We present evidence that the p37 gene is part of an operon encoding two additional proteins which are highly similar to components of the periplasmic binding-protein-dependent transport systems of Gram-negative bacteria, and we suggest that p37 is part of a homologous, high-affinity transport system in M. hyorhinis, a Gram-positive bacterium. We discuss the influence of p37 and M. hyorhinis on contact inhibition of locomotion of mammalian cells. UI: 89091146

TITLE: A mycoplasmal protein influences tumour cell invasiveness and contact inhibition in vitro. Authors: Dudler R, Schmidhauser C


ABSTRACT: Fab fragments of a monoclonal antibody directed against p37, a protein associated with the surface of FS9 mouse sarcoma cells, were previously found to inhibit the highly invasive behaviour of FS9 cells in vitro. We show that p37 originates from Mycoplasma hyorhinis. Infecting various cell lines with the mycoplasma consistently increased their invasiveness when confronted with chicken heart fibroblasts using Abercrombie’s confronted explant technique. Conversely, removing the mycoplasmas or blocking p37 with specific Fab fragments reduced invasiveness. Analysis of individual cell collisions using time-lapse filming showed that the addition of Fab fragments to cells infected with M. hyorhinis greatly increased the level of contact inhibition. The antibody also reduced the invasiveness of transformed cells that did not express the p37 antigen. Hence, a cellular protein or proteins that are structurally related to p37 apparently influence invasive behavior.

ARTICLE: Bacteria - Commensales or Cofactor of Oncogenesis? by Ferdinand Ruzicka

[NOTE: This recent internet article reflects German research originally published in 1983; see: F.Ruzicka: Mykoplasmen-Kommensalen oder Kofaktor bei der Onkogenese? Eigenverlag, Wien 1983]

Discussion.
Bacterial infections are a major problem in cancer patients. Bacteria isolated from blood cultures are either Gram-positive or Gram-negative such as Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Acinetobacter species, Enterobacteriaceae and others. Another group of bacteria which can be isolated from blood cultures of cancer patients are mycoplasmas such as M.pulmonis, M. fermentans, M.hominis, M.salivarium and others.

Of interest in this connection are also the hemotrophic bacteria, the families Bartonellaceae and Anaplasmataceae. Organisms of the various genera of the family Anaplasmataceae are all quite similar morphologically and are similar morphologically to mycoplasmas and L-phase bacteria, cell wall-defective bacterial
Studies by Domingue et al. (1976) describe the recovery of variant and wall-defective bacterial forms from the blood of normal as well as diseased humans.

We have first published in 1983 about a group of very small bacteria isolated from peripheral blood under the suggested name "basoplasmas" or "Basoplasma sanguineum". These very small bacteria had a mean diameter of 0.25\mu m, some of them had a cell wall, others were cell-wall-deficient bacteria, either L-forms or mycoplasmas (Ruzicka,1983). Another difference to the usually found bacteria was that they were alkaliphiles. Alkaliphiles are micro-organisms which require alkaline pH > 10 and show a considerable growth at pH of around 10. Alkaliphiles have been isolated mainly from neutral environments, from soil samples of neutral pH, sometimes even from acidic soil samples. However, they should be considered as extremophiles, even though they can be isolated from normal environments because of their alkaliphily. In this connection the most interesting bacterium is the soil bacterium Agrobacterium tumefaciens that grows in soil with pH=12 and infects the roots and stems of dicotyledonous plants resulting in cancerous growth (galls).

Kajander et al. 1994 isolated tiny bacteria from human blood. They can pass through sterile filters and endure g-irradiation like a virus (1 mega rad). Their size is between that of a virus and cell-walled bacteria. Their suggested name is "Nanobacterium sanguineum". They produce a slimy biomatrix that forms carbonate apatite mineral around them in culture (Kajander, 1998). Fig.1B,C,D Kajander et al. 1994 and Fig.4A, Kajander, 1998 show TEM photomicrographs of cultured "Nanobacterium sanguineum or sanguineum" similar morphologically to TEM photomicrographs of tiny bacteria we isolated from human blood (fig. 10a) called 'basoplasmas', Ruzicka,1983. Our fig.3b show a nanocolony of these tiny bacteria, partly dividing and crystals between the bacteria comparable with apatit crystals we observed in dental calculus (Ruzicka,1983, 1984). We suggested that these nano colonies are growing in erythrocytes, because we could see similar structures within erythrocytes by light microscopy.

With an "anti-ca" FITC we detected the small bacteria in freeze sectioned cancer tissue and in blood smears of cancer patients but rarely in the control group(Ruzicka,1983). Ciftcioglu and Kajander, 1998 showed that many malignant cells have receptors for "nanobacterial" adherence. An animal experiment showed that from 18 mice with subcutaneous injection of 0.1ml particle ("basoplasmas") suspension 28% fall ill with cancer. 39% had chronic inflammations and 67% had granulocytosis. One mouse from the control had an adenoma of the lung and one an osteoma that are 17%, the other mice were healthy (Ruzicka,1983).

As a conclusion of our results we think that these small bacteria are a cofactor of oncogenesis and not a commensal. (highlight by CA homepage). Our supposition is that these facultative alkaliphilic and hemotrophic 0.25\mu m bacteria called by us (Ruzicka, 1983) "basoplasmas" or "Basoplasma sanguineum sp. nov." first infects erythrocytes. A possible pathway of infection are ticks. Erythrocytes have no nucleus and therefore their transformation is not possible. If the number of "basoplasmas" after their multiplication within erythrocytes is high enough they
infects other human tissues. Infection is directed by a tumour inducing (Ti) plasmid, by the insertion of specific genes (T-DNA) into the genome of infected human cells.