［特別報告］

フッ化ナトリウム（NaF）の変異原性について
——文献的考察とヒトのリンパ球による検定——

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フッ素の利用に批判的な立場の教員からの依頼で染色体異常試験を行った。その結果、フッ素はむし歯予防のための塗布や洗口に用いられる濃度でも、ヒト培養リンパ球に染色体異常を誘発することを認めた。

得られた試験結果を基に文献的考察を行って、フッ素は安全性が保証されているわけではないと結論した。

Genetic Effects of Sodium Fluoride (NaF)
— Review and Human Lymphocyte Assay —

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Clastogenic activity of sodium fluoride in great ape cells

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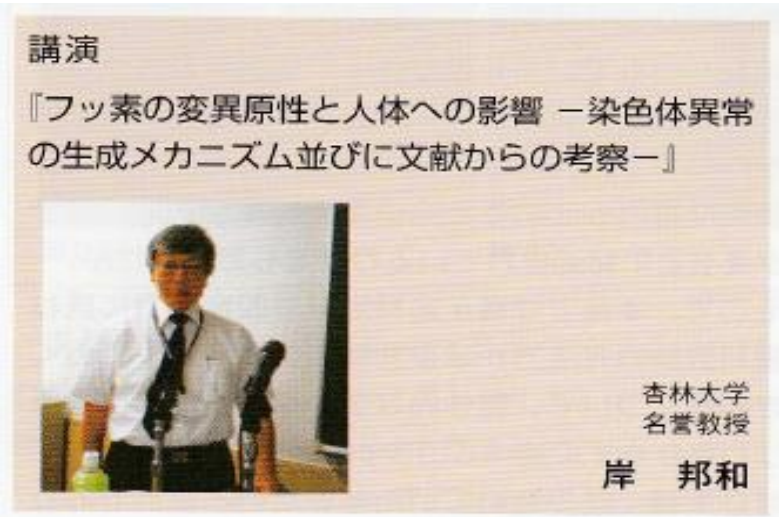
Summary

Conflicting evidence has been reported concerning the mutagenicity of sodium fluoride (NaF), especially clastogenicity at concentrations of more than 1 mM. NaF is known to induce chromosome aberrations at these concentrations in human cells, but not in most rodent cells. We considered that such species-specific difference in chromosomal sensitivity would be derived from the phylogenetic distance between rodents and man. To clarify the role of interspecies differences, we investigated the chromosomal sensitivity to NaF in cell lines from various primates, which diverged into many species, including rodent-like prosimians and human-like great apes. The results showed that the clastogenicity of NaF was limited to human and great ape cells.

フッ素の染色体異常誘発作用が、ヒトには認められるがげっ歯類を用いた多くの研究では認められないため、原猿から類人猿までの霊長類由来の細胞を用いて、染色体感受性をしらべた。その結果、フッ素の染色体異常誘発はヒトと類人猿にのみ観察された。



フッ素の誘発する染色体異常の形態学的特徴から、フッ素がDNA合成を阻害することによって染色体異常を誘発していると推測された。
塗布や洗口に用いられる高いフッ素濃度では、口腔内あるいは胃でDNA合成を行っている細胞に染色体異常を誘発する可能性はある。しかしその数は極めて少数であり、染色体異常が誘発されてなお生存可能な細胞はさらに少数であると考えられる。

フッ素はDNAに塩基損傷を誘発する作用基をもたないので、血中で希釈されると他の臓器での染色体異常の誘発はないと考えらる。
従って、フッ素が発ガン性や遺伝毒性を有する可能性は低いと結論した。

類似のDNA合成阻害剤の発ガン性や遺伝毒性についてのデータが蓄積されているが、今なお陽性と判断されていない。
上述の結論は国際的な理解と軌を一にするものと考える。

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Evidence for Excision Repair-Dependent and -Independent Processes in Ara C-Induced Chromosome Rearrangements in G_1 Human Lymphocytes

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1-β-D-arabinofuranosylcytosine (ara C) enhances the formation of chromosome rearrangements such as translocations or dicentric chromosomes in G_1 cells containing DNA lesions. The formation of rearrangements is hypothesized to be the result of inhibition of excision repair. Ara C has also been known to lead to the formation of chromosome rearrangements in G_1 cells in the absence of induced DNA lesions. It is not known whether a common mechanism is involved in these two processes. In the present study, we used excision repair-deficient XP cells to investigate whether excision repair is involved in the formation of chromosome rearrangements in G_1 cells which do not contain induced DNA lesions.

G_0 Lymphocytes from an XP patient were either treated with 4-nitroquinoline-1-oxide (4NQO) or left untreated. Cells were then cultured in the presence of ara C for about 18 h. Aphidicolin (APC), which induces chromosome rearrangements in cells containing 4NQO-induced DNA lesions, was used for comparison. The resulting frequency of dicentrics and rings (dic & ring) was determined at the first mitoses after culture initiation. In 4NQO-pretreated XP cells, the frequency of dic & ring was not increased by post-treatment with ara C or with APC. This result is thought to reflect the absence of excision repair in XP cells. However, normal induction of dic & ring was observed in XP cells not pretreated with 4NQO but treated with ara C.

Thus, there seems to be two different processes involved in the induction of G_1 rearrangements: excision repair-dependent and excision repair-independent. UV-endonuclease is not involved in excision repair-independent rearrangements. © 1993 Wiley-Liss, Inc.

Key words: Chromosome abberaions in vitro, DNA repair inhibition, human cultured lymphocytes, xeroderma pigmentosum cells

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Suppressive effect of novobiocin on the frequency of chromosome-type aberrations induced by ara C in the G_1 phase of human lymphocytes

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Keywords: Novobiocin; Ara C; Chromosome-type aberrations; Human lymphocytes; Repair inhibition

Summary

1-β-D-Arabinofuranosylcytosine (ara C) induces chromosome-type aberrations in mammalian cells by inhibiting repair replication in the G_1 phase. The effect of novobiocin, an inhibitor of prokaryotic gyrases, on G_1 repair in human cells was studied cytogenetically using this characteristic of ara C. The experiment was based on the assumption that if novobiocin inhibits the relaxation of chromatin required prior to repair replication, it would reduce the frequency of chromosome-type aberrations in cells treated with a mutagen followed by posttreatment with ara C. It has also been shown that in lymphocytes ara C induces chromosome-type aberrations which were not caused by any induced DNA lesion, and that the frequency of these aberrations changes with the age of the blood donor. The effect of novobiocin on the frequency of chromosome-type aberrations induced by ara C in lymphocytes without mutagen pretreatment was also investigated for blood samples from donors of different ages.

Human peripheral blood lymphocytes, which were either untreated of treated with 4-nitroquinoline-*N*-oxide (4NQO) or methyl methanesulfonate (MMS), were posttreated in their early G_1 phase with ara C only or ara C and novobiocin. The resulting chromosome-type aberrations were observed in cells in their first mitoses, and a comparison was made between the frequency of aberrations occurring in the presence of novobiocin and in its absence.

The results showed that novobiocin reduced the frequency of chromosome-type aberrations induced by ara C in both mutagen-pretreated and -non-pretreated cells, and that lymphocytes from younger donors were less sensitive to novobiocin. The present study demonstrated cytogenetically the existence of a novobiocin-sensitive process to induce chromosome recombination in G_1 lymphocytes.

ヒト細胞の染色体異常誘発機構は複雑な過程であり、その研究には、DNA損傷誘発物質、DNA合成阻害剤、修復欠損細胞などを包括的に利用することが必要である。

仮説に基づいた戦略的な実験を通じて得た結果から、さらに仮説をリファインしてヒトにおける染色体異常生成機構に迫ることができた。

この結果は、染色体異常に関する国際シンポジウムの招待講演で発表した。

概要は以下の通り。様々なDNA損傷誘発物質とDNA修復阻害剤を組み合わせて、誘発された染色体異常の頻度を比較した。その結果、DNAポリメラーゼαが異常の生成に関与していることが示唆された。さらに、DNAジャイレースの阻害が関与していることも明らかになった。

Radiation-Induced Chromosome Damage in Man, pages 605–616
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28

Types and Frequencies of Chromosome Aberrations in Peripheral Lymphocytes of General Populations

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Peripheral blood lymphocytes from 96 adults of various age groups have been investigated to determine the types and frequencies of spontaneous chromosome aberrations. None of the subjects previously had received any occupational exposure or significant irradiation from medical examinations. In addition, blood samples from 48 newborn infants were examined. In the adult groups, the frequencies of chromatid gaps and breaks were found to be independent of sex and age. The mean frequency of chromatid exchanges was 0.8×10^{-3} for the adult groups and 0.2×10^{-3} for newborns. The mean frequencies of dicentric aberrations, acentric fragments, and cells with unstable aberrations (Cu cells) increased with advancing age, but no age effect was observed in the cells with stable aberrations (Cs cells). The analysis of the incidence of dicentrics showed a linear increase with age. The estimated rate of increase was 1.70×10^{-4} at the 10-y interval. In the female groups the frequency of hyperdiploid cells increased exponentially with age, whereas no such pattern of increase was observed in the male groups. These results were compared with other published data for spontaneous chromosome aberrations in control subjects.