抗腫瘍性トロポロン誘導体処理によるマウス乳癌細胞FM3Aにおけるデオキシヌクオシド三リン酸の不均衡とDNA二重鎖開裂

大和正利*, 広田康秀*, 吉田　聖*, 田中章平*, 森田哲生,
酒井潤子*, 橋垣国子*, 早津彦哉*, 綿田有佑*

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Imbalance of Deoxyribonucloside Triphosphates and DNA Double-strand Breaks in Mouse Mammary FM3A Cells Treated in vitro with an Antineoplastic Tropolone Derivative

Masatoshi Yamato*, Yasuhide Hirota*, Sei Yoshida*
Shouhei Tanaka*, Tetsuo Morita, Junko Sakai*
Kuniko Hashigaki*, Hikoya Hayatsu* and Yusuke Wataya*

ABSTRACT The mechanism by which α, α-bis(2-hydroxy-6-isopropyltropon-3-yl)-4-methoxytoluene (JCI-3661) kills mouse mammary tumor FM3A (F28-7) cells was studied. When the cells were exposed to the drug at 3.7 μ*M*, the intracellular dNTP pool became imbalanced because of decreases in dGTP and dATP and an increase in dTTP. The pattern of the dNTP imbalance was the same as that caused by hydroxyurea. When JCI-3661 was added to the culture medium, mature DNA strands broke, giving fragments of 100-200 kilobase pairs long as found by orthogonal-field-alternation gel electrophoresis. DNA strand breaks, detected by this technique, were observed in the cells at 12 h after the addition. The beginning of cell death was observed at about 14 h (trypan blue staining) or at about 12 h (colony-forming ability) after cultivation Breaks in the single and double strands of DNA, as measured by alkaline and neutral filter elution assay, became evident 24 h after treatment with 3.7 μ*M* JCI-3661. Comparison of the ratio of single-and double-strand breaks caused by JCI-3661 to that following radiation suggested that JCI-3661 broke only double strands. Cycloheximide inhibited both the breakage of double strands and the cell death caused by JCI-3661. JCI-3661 decreased DNA

synthesis more than RNA or protein synthesis. The breaks in double strands of DNA were probably important in the cell death caused by JCI-3661.

抄録　α, α-bis(2-hydroxy-6-isopropyltropo-3-yl)-4-methoxytoluene（JCI-3661）の乳癌FM3A細胞に対する作用について解析した。本剤の処理により細胞内デオキシリボヌクレオシド三リン酸プールは不均衡を生じ，これは，リボヌクレオチド還元酵素阻害剤ヒドロキシ尿素で処理した際と，ほぼ同じであった。またこの処理により，DNAの二重鎖開裂が認められ，これらがJCI-3661によって引き起こされる細胞死に重要な役割を果しているものと考えられる。

* 岡山大学薬学部（Fac. Pharm, Sci., Okayama Univ.）