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Possible Role of Polyamine on Tumor Spread after Surgical Trauma

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***Abstract*—**Surgical trauma seems to facilitate metastatic spread, although the underlying mechanisms are not known. Increased concentrations of polyamines (spermine and spermidine) in the blood seem to have associated with the enhanced malignant potential of cancer cells and decrease in anti-tumor immunity of cancer patients. In addition to de novo synthesis in rapidly growing cells such as normal regenerating cells and cancer cells, cells can take up polyamines from extra-cellular sources. We have shown that increased polyamine concentration results in decreases in cytokine production and expression of adhesion molecules involved in anti-tumor immunity, such as CD11a. And, immune cells in an environment with increased polyamine levels lose anti-tumor immune functions, such as lymphokine activated killer cell (LAK) activities. Because blood polyamine levels are increased in post-surgical patients, polyamine seems to have roles on post-traumatic tumor spread.

***Keywords*—**Immune function, LAK, Polyamine, Surgical trauma.

I. Introduction

POLYAMINE (spermidine and spermine) are polycations with three or four amine groups. Almost all cells can produce polyamines, but their production is especially high in rapidly growing cells such as cancer cells. Polyamine concentrations are often increased in the blood and urine of cancer patients. The increased blood and urinary polyamine levels are attributable to increased polyamine synthesis by cancer cells, since these increases can be abolished by complete eradication of tumors by surgery or radio-chemotherapy [1]-[4]. Because polyamines act as growth factor, increased polyamine availability is one of the factors that accelerate tumor growth. Actually, increased polyamine levels in blood and urine in cancer patients have been shown to correlate with poor prognosis [5].

We have shown that polyamine, especially spermine, suppresses production of pro-inflammatory cytokines such as tumor necrosis factor (TNF) and decreases expression of lymphocyte function associate antigen-1 (LFA-1) on immune cell [6], [7]. TNF, a member of a group of cytokines that can cause cell death, is a cytokine involved in cell killing, and LFA-1 is a very important protein expressed on cell membrane and crucial for the activation of immune cells. These suggest possible role of polyamine on suppressed immune function observed in cancer patients, and we have shown that the increase in polyamine levels in immune cells decreased lymphokine-activated killer cell (LAK) activities [8]. LAK activities, generated in vitro by culture of peripheral blood mononuclear cells (PBMCs) in interleukin 2 (IL-2), have potent cytotoxic ability against tumor cells.

Blood concentration and urinary excretion of polyamines are known to increase after surgery, although the origin of this increase is not well established [9], [10]. In this article, the possible role of polyamine on post-traumatic tumor spread is discussed.

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II. What Are Polyamines?

The natural polyamines, spermidine and spermine, are found in almost every living cell at high micromolar to low millimolar quantities [11]. They are indispensable for cell growth and differentiation and have many biological activities [12]-[15]. Polyamines are synthesized from arginine and s-adenosylmethionine with arginase converting arginine to ornithine, and ornithine decarboxylase (ODC) catalyzing ornithine decarboxylation to form putrescine, a polyamine precursor containing two amine groups (Fig. 1). Generally, the enzymatic activities for polyamine synthesis in normal cells decrease with aging.

Intracellular spermine and spermidine are degraded by a highly inducible enzyme, spermidine/spermine N1-acetyltransferase (SSAT), and N1-acetylpolyamine oxidase (APAO). SSAT catalyzes the transfer of an acetyl group from acetyl-coenzyme A to the aminopropyl moiety of spermine and spermidine. APAO preferentially catalyzes the oxidation of the N1-acetylspermine and N1-acetylspermidine produced by SSAT activity.

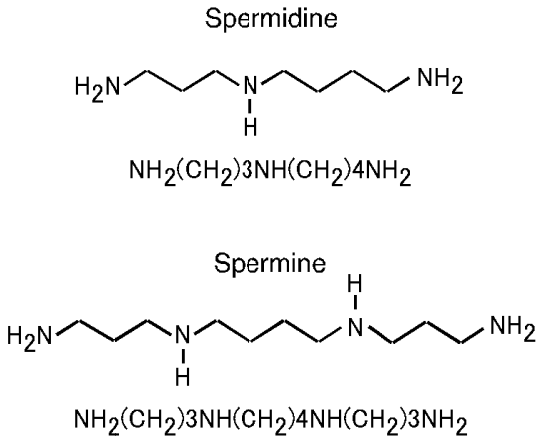

Fig. 1 Polyamines (spermine and spermidine)

In addition to de novo synthesis and degradation, cellular polyamine concentrations are also regulated by transmembrane transport where cells take up polyamines from their surroundings or export them to the extracellular space [16], [17].

III. Polyamines in the Body

Polyamines produced somewhere in the body are transported to various organs and tissues. For example, polyamines in the intestinal lumen are absorbed quickly in their original forms because there is no apparent enzymatic activity present to catalyze their degradation and distributed to all organs and tissues [18]-[20]. However, short-term increased polyamine intake failed to produce such increases [21]-[23], possibly because of the homeostasis that inhibits acute changes in intracellular polyamine concentration. Increased blood polyamine levels in animals and humans produced in response to continuous enhanced polyamine intake [21], [22]. Conversely, reductions in blood polyamine concentration were not achieved only by restricting oral polyamine intake. Decrease in blood polyamine levels can be successfully achieved by eliminating intestinal microbiota in addition to restricting food polyamines [24]-[26]. These indicate that at least two sources of intestinal polyamines are postulated: foods and intestinal microbiota.

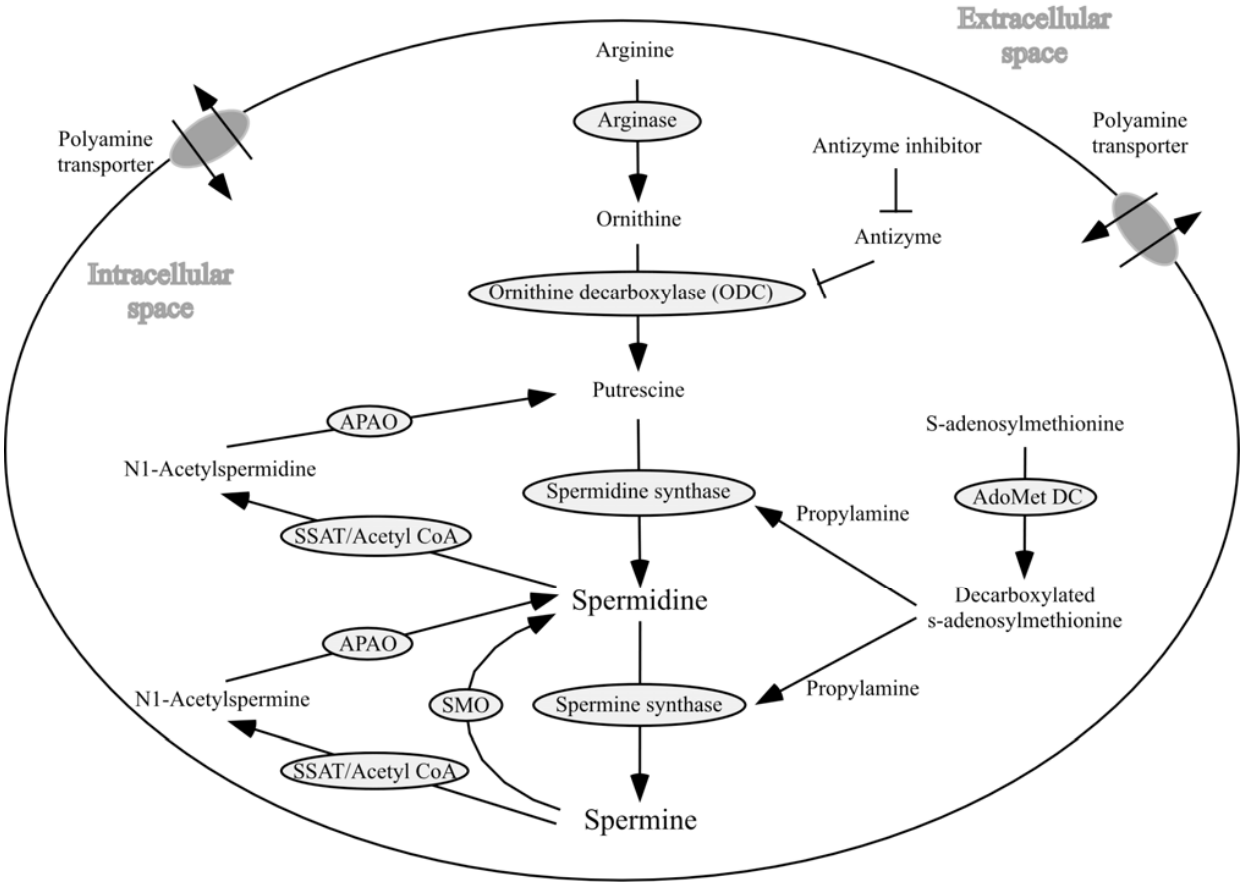

Fig. 2 Polyamine synthesis and degradation AdoMetDC = S-adenosylmethionine decarboxylase, APAO = N1-acetylpolyamine oxidase, SMO = spermine oxidase,SSAT = spermine/spermidine N1-acetyltransferase

Similarly, numerous reports have shown that both blood and urine polyamine concentrations are often increased in cancer patients [4], [11], [27]-[29]. A close correlation between blood polyamine levels and the amount of urinary polyamines has also been found in cancer patients [5]. These levels decrease after tumor eradication and increase after relapse [1], [2], [4], [27], [30], indicating that polyamines synthesized by cancer tissues are transferred to the blood circulation and kidney, where they are excreted into the urine [31].

Taken together, polyamines produced somewhere in the body, such as cancer tissues and intestinal lumen, appear to influence polyamine levels in the blood. In blood circulation, the majority of polyamines are contained in blood cells, especially in red and white blood cells, and therefore increases in blood polyamine concentration indicate concurrent increases in polyamine levels in blood cells [32].

IV. Possible Role of Polyamine on Post-Traumatic Tumor Spread

Trauma, such as surgery, is itself considered to increase the risk of cancer spread through various mechanisms [33]-[35]. Blood concentration and urinary excretion of polyamines are known to increase after surgery even in patients with no neoplastic growth [9], [10]. Although the origin of this increase is not well established, at least two sources, i.e. intestinal lumen and regenerating tissues, can be considered.

Dietary intake is inhibited or restricted during medical-treatment and after surgical trauma. Reduction of dietary intake means reduction of the polyamine supply from food. Moreover, the peri-operative antibiotic damages intestinal bacteria and suppresses the polyamine synthesis. Therefore, resumption of the meal after trauma will result in increased polyamine supply from intestinal lumen originated in food and intestinal microbiota. In addition, the enzymatic activities for polyamine synthesis increase significantly at tissues where there was a surgical trauma [36]-[39]. These indicate that the polyamine supply from intestinal lumen and/or regenerating tissues have contributed the rise of the postoperative polyamine concentration in blood [9].

Our previous study showed that increases in blood polyamine levels are inversely associated with anti-tumor cytotoxicities of LAK in patients who have undergone surgery [8]. LAK activities, involved in the killing of established tumor in the body, are often decreased in cancer patients [40]-[43]. In addition to mechanisms previously postulated for post-traumatic cancer spread, post-operative increases in blood polyamine levels and resultant decrease in activities of LAK may be another factor that accelerates tumor growth.

V. Conclusion

Post-traumatic increase in polyamine concentrations in blood may be one of the factors that inhibit anti-tumor immune function and resultant acceleration of tumor spread.

References

[1] C. Loser, U. R. Folsch, C. Paprotny, and W. Creutzfeldt, "Polyamines in colorectal cancer. Evaluation of polyamine concentrations in the colon tissue, serum, and urine of 50 patients with colorectal cancer," Cancer, vol. 65, no. 4, pp. 958-966, 1990.

[2] M. Chatel, F. Darcel, V. Quemener, H. Hercouet, and J. P. Moulinoux, "Red blood cell polyamines as biochemical markers of supratentorial malignant gliomas," Anticancer Res,vol. 7, no. 1, pp. 33-38, 1987.

[3] S. Kubota, Z. Yamasaki, M. Yoshimoto, N. Murata, T. Wada, N. Ohsawa, and F. Takaku, "The value of urinary polyamine assay in stomach cancer. Comparison with serum carcinoembryonic antigen," Cancer,vol. 56, no. 7, pp 1630-1635, 1985.

[4] N. Uehara, S. Shirakawa, H. Uchino, and Y. Saeki, "Elevated contents of spermidine and spermine in the erythrocytes of cancer patients," Cancer,vol. 45, no. 1, pp 108-111, 1980.

[5] B. G. Durie, S. E. Salmon, and D. H. Russell, "Polyamines as markers of response and disease activity in cancer chemotherapy," Cancer Res,vol. 37, no. 1, pp 214-221, 1977.

[6] K. Soda, Y. Kano, T. Nakamura, K. Kasono, M. Kawakami, and F. Konishi, "Spermine, a natural polyamine, suppresses LFA-1 expression on human lymphocyte," J Immunol,vol. 175, no. 1, pp 237-245, 2005.

[7] K. Soda, Y. Kano, T. Nakamura, Kawakami, and F. Konishi, "Spermine and spermidine induce some of the immune suppression observed in cancer patients," Annals of Cancer Research and Therapy,vol. 11, no. 1&2, pp 243-253, 2003.

[8] Y. Kano, K. Soda, T. Nakamura, M. Saitoh, M. Kawakami, and F. Konishi, "Increased blood spermine levels decrease the cytotoxic activity of lymphokine-activated killer cells: a novel mechanism of cancer evasion," Cancer Immunol Immunother, vol.56, no. 6, pp 771-781, 2007.

[9] K. Nishioka, M. M. Romsdahl, and M. J. McMurtrey, "Serum polyamine alterations in surgical patients with colorectal carcinoma," J Surg Oncol, vol.9, no. 6, pp 555-562, 1977.

[10] T. Tsukamoto, H. Kinoshita, K. Hirohashi, S. Kubo, and S. Otani, "Human erythrocyte polyamine levels after partial hepatectomy," Hepatogastroenterology, vol. 44, no. 15, pp 744-750, 1997.

[11] D. H. Russell, "Clinical relevance of polyamines," Crit Rev Clin Lab Sci, vol. 18, no. 3, pp. 261-311, 1983.

[12] J. Hochman, A. Katz, and U. Bachrach, "Polyamines and protein kinase II. Effect of polyamines on cyclic AMP--dependent protein kinase from rat liver," Life Sci, vol. 22, no. 17, pp. 1481-1484, 1978.

[13] A. Tabib, and U. Bachrach, "Activation of the proto-oncogene c-myc and c-fos by c-ras: involvement of polyamines," Biochem Biophys Res Commun, vol. 202, no. 2, pp 720-727, 1994.

[14] C. A. Panagiotidis, S. Artandi, K. Calame, and S. J. Silverstein, "Polyamines alter sequence-specific DNA-protein interactions," Nucleic Acids Res, vol. 23, no. 10, pp. 1800-1809, 1995.

[15] A. C. Childs, D. J. Mehta, and E. W. Gerner, "Polyamine-dependent gene expression," Cell Mol Life Sci, vol. 60, no. 7, pp. 1394-1406, 2003.

[16] L. D'Agostino, S. Pignata, B. Daniele, G. D'Adamo, C. Ferraro, G, Silvestro, P. Tagliaferri, A. Contegiacomo, R. Gentile, G. Tritto, A. R. Bianco, and G. Mazzacca, "Polyamine uptake by human colon carcinoma cell line CaCo-2," Digestion, vol. 46, Suppl 2, pp. 352-359, 1990.

[17] J. J. Feige, and E. M. Chambaz, "Polyamine uptake by bovine adrenocortical cells," Biochim Biophys Acta, vol. 846, no. 1, pp. 93-100, 1985.

[18] S. Bardocz, D. S. Brown, G. Grant, and A. Pusztai, "Luminal and basolateral polyamine uptake by rat small intestine stimulated to grow by Phaseolus vulgaris lectin phytohaemagglutinin in vivo," Biochim Biophys Acta, vol. 1034, no. 1, pp. 46-52, 1990.

[19] D. L. Osborne, and E. R. Seidel, "Gastrointestinal luminal polyamines: cellular accumulation and enterohepatic circulation," Am J Physiol, vol. 258, no. 4 Pt 1, pp. G576-G584, 1990.

[20] M. Kobayashi, Y. J. Xu, K. Samejima, H. Goda, M. Niitsu, M. Takahashi, Y. and Hashimoto, "Fate of orally administered 15N-labeled polyamines in rats bearing solid tumors," Biol Pharm Bull, vol. 26, no. 3, pp. 285-288, 2003.

[21] K. Soda, Y. Kano, M. Sakuragi, K. Takao, A. Lefor, and F. Konishi, "Long-term oral polyamine intake increases blood polyamine concentrations," J Nutr Sci Vitaminol (Tokyo), vol. 55, no. 4, pp. 361-366, 2009.

[22] K. Soda, Y. Dobashi, Y. Kano, S. Tsujinaka, and F. Konishi, "Polyamine-rich food decreases age-associated pathology and mortality in aged mice," Exp Gerontol, vol. 44, no. 11, pp. 727-732, 2009.

[23] B. P. Brodal, K. A. Eliassen, H. Ronning, and H. Osmundsen, "Effects of dietary polyamines and clofibrate on metabolism of polyamines in the rat," J Nutr Biochem, vol. 10, no. 12, pp. 700-708, 1999.

[24] S. Sarhan, M. Weibel, and N. Seiler, "Effect of polyamine deprivation on the survival of intracranial glioblastoma bearing rats," Anticancer Res, vol. 11, no. 2, pp. 987-992, 1991.

[25] N. Seiler, S. Sarhan, C. Grauffel, R. Jones, B. Knodgen, and J. P. Moulinoux, "Endogenous and exogenous polyamines in support of tumor growth," Cancer Res, vol. 50, no. 16, pp. 5077-5083, 1990.

[26] B. G. Cipolla, R. Havouis, and J. P. Moulinoux, "Polyamine reduced diet (PRD) nutrition therapy in hormone refractory prostate cancer patients," Biomed Pharmacother, vol. 64, no. 5, pp. 363-368, 2010.

[27] S. Kubota, M. Okada, M. Yoshimoto, N. Murata, Z. Yamasaki, T. Wada, K. Imahori, N. Ohsawa, F. Takaku, "Urinary polyamines as a tumor marker," Cancer Detect Prev, vo. 8, no. 1-2, pp. 189-192, 1985.

[28] T. S. Weiss, G. Bernhardt, A. Buschauer, W. E. Thasler, D. Dolgner, H. Zirngibl, and K. W. Jauch, "Polyamine levels of human colorectal adenocarcinomas are correlated with tumor stage and grade," Int J Colorectal Dis, vol. 17, no. 6, pp. 381-387, 2002.

[29] M. Linsalata, M. G. Caruso, S. Leo, V. Guerra, B. D'Attoma, and A. Di Leo, "Prognostic value of tissue polyamine levels in human colorectal carcinoma," Anticancer Res, vol. 22, no. 4, pp. 2465-2469, 2002.

[30] A. N. Kingsnorth, A. B. Lumsden, and H. M. Wallace, "Polyamines in colorectal cancer," Br J Surg, vol. 71, no. 10, pp. 791-794, 1984.

[31] J. P. Moulinoux, V. Quemener, N. A. Khan, J. G. Delcros, and R. Havouis, “Spermidine uptake by erythrocytes from normal and Lewis lung carcinoma (3LL) grafted mice: I. In vitro study,” Anticancer Res, vol. 9, no. 4, pp. 1057-1062, 1989.
[32] K. D. Cooper, J. B. Shukla, and O. M. Rennert, “Polyamine compartmentalization in various human disease states,” Clin Chim Acta, vol. 82, no. 1-2, pp. 1-7, 1978.
[33] G. G. Page, S. Ben-Eliyahu, and J. C. Liebeskind, “The role of LGL/NK cells in surgery-induced promotion of metastasis and its attenuation by morphine,” Brain Behav Immun, vol. 8, no. 3, pp. 241-250, 1994.
[34] R. E. Pollock, G. F. Babcock, M. M. Romsdahl, and K. Nishioka, “Surgical stress-mediated suppression of murine natural killer cell cytotoxicity,” Cancer Res, vol. 44, no. 9, pp. 3888-3891, 1984.
[35] T. Hattori, Y. Hamai, T. Harada, H. Ikeda, and T. Ikeda, “Enhancing effect of thoracotomy and/or laparotomy on the development of the lung metastases in rats after intravenous inoculation of tumor cells,” Jpn J Surg, vol. 7, no. 4, pp. 263-268, 1977.
[36] S. Kubo, I. Matsui-Yuasa, S. Otani, S. Morisawa, H. Kinoshita, and K. Sakai, “Effect of splenectomy on liver regeneration and polyamine metabolism after partial hepatectomy,” J Surg Res, vol. 41, no. 4, pp. 401-409, 1986.
[37] G. D. Luk, “Essential role of polyamine metabolism in hepatic regeneration. Inhibition of deoxyribonucleic acid and protein synthesis and tissue regeneration by difluoromethylornithine in the rat,” Gastroenterology, vol. 90, no. 5 Pt 1, pp. 1261-1267, 1986.
[38] H. S. Beyer, M. Ellefson, R. Sherman, and L. Zieve, “Aging alters ornithine decarboxylase and decreases polyamines in regenerating rat liver but putrescine replacement has no effect,” J Lab Clin Med, vol. 119, no. 1, pp. 38-47, 1992.
[39] A. E. Mautes, W. Paschen, G. Rohn, and A. C. Nacimiento, “Changes in ornithine decarboxylase activity and putrescine concentrations after spinal cord compression injury in the rat,” Neurosci Lett, vol. 264, no. 1-3, pp. 153-156, 1999.
[40] C. M. Balch, K. Itoh, and A. B. Tilden, “Cellular immune defects in patients with melanoma involving interleukin-2-activated lymphocyte cytotoxicity and a serum suppressor factor,” Surgery, vol. 98, no. 2, pp. 151-157, 1985.
[41] G. G. Hermann, K. R. Petersen, K. Steven, and J. Zeuthen, “Reduced LAK cytotoxicity of peripheral blood mononuclear cells in patients with bladder cancer: decreased LAK cytotoxicity caused by a low incidence of CD56+ and CD57+ mononuclear blood cells,” J Clin Immunol, vol. 10, no. 6, pp. 311-320, 1990.
[42] N.L. Wood, E. N. Kitces, and W. K. Blaylock, “Depressed lymphokine activated killer cell activity in mycosis fungoides. A possible marker for aggressive disease,” Arch Dermatol, vol. 126, no. 7, pp. 907-913, 1990.
[43] J. Funk, G. Schmitz, K. Failing, and E. Burkhardt, “Natural killer (NK) and lymphokine-activated killer (LAK) cell functions from healthy dogs and 29 dogs with a variety of spontaneous neoplasms,” Cancer Immunol Immunother, vol. 54, no. 1, pp. 87-92, 2005.