

# 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

**P**OLYAMINE (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.

## 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.

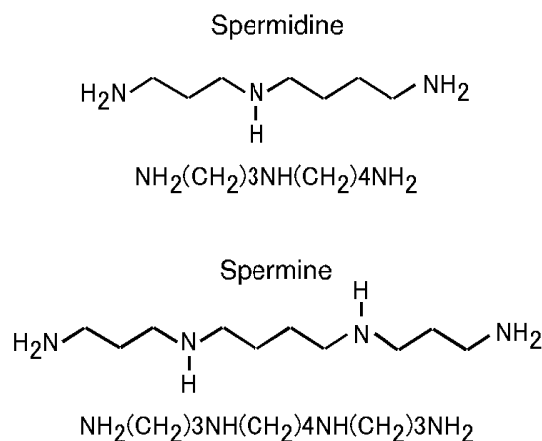


Fig. 1 Polyamines (spermine and spermidine)

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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.

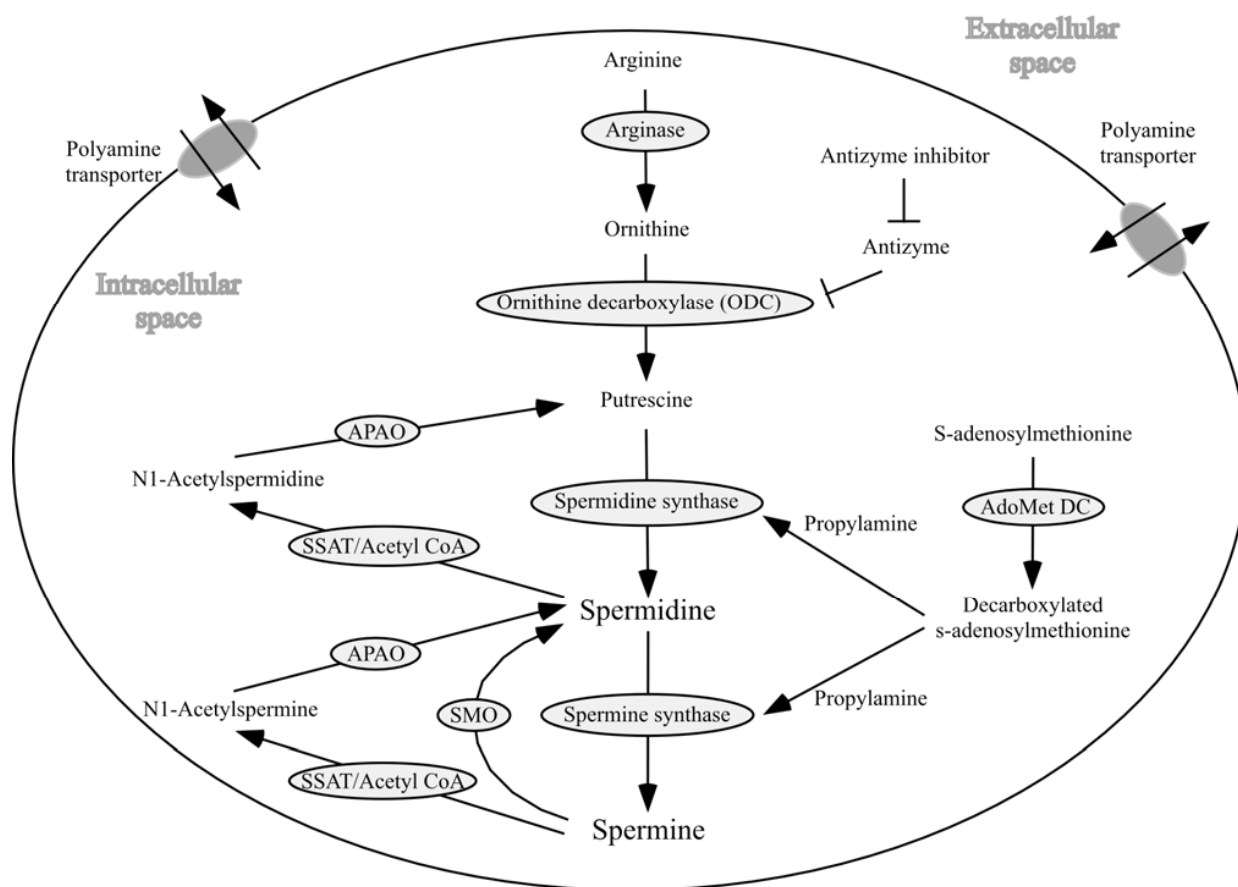


Fig. 2 Polyamine synthesis and degradation AdoMetDC = S-adenosylmethionine decarboxylase, APAO = N1-acetylpolyamine oxidase, SMO = spermine oxidase, SSAT = spermine/spermidine N1-acetyltransferase

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.

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