An emerging role for agmatine

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An emerging role for agmatine. Polyamines, required components of proliferation, are autoregulated by the protein antizyme. To date, agmatine is the only molecule other than the polyamines that can induce antizyme, and thus influence cell homeostasis and growth. Agmatine has effectively suppressed proliferation in immortalized and transformed cell lines. An increased sensitivity to the anti-proliferative effects of agmatine observed in Ras transformed versus native cells paralleled an increase in agmatine uptake in the transformed cells. We hypothesize that agmatine may target transformed cells via selective transporters.

Polyamines (putrescine, spermidine, and spermine) are small ubiquitous cationic molecules required for cell homeostasis and growth [1, 2]. Polyamine biosynthesis is regulated throughout the cell cycle, resulting in augmented intracellular polyamine levels [3]. As such, polyamines have been described to play an important role in the transformation process [4-8]. Conversely, the depletion of intracellular polyamines results in the suppression of growth [9, 10]. In spite of the need for polyamines for cell cycle progression, their specific regulatory roles in this capacity have yet to be fully resolved.

Intracellular polyamine concentrations are autoregulated by the induction of the protein antizyme [11]. Antizyme is the only known endogenous protein that binds to the first rate-limiting enzyme of polyamine biosynthesis, ornithine decarboxylase (ODC), inhibiting its activity and accelerating its degradation [12]. In addition to inhibiting polyamine biosynthesis, antizyme has been shown to concurrently suppress polyamine transporters [13, 14]. Because of this unique, two-pronged negative feedback system, antizyme is an effective endogenous protein in limiting intracellular polyamine levels.

Agmatine is a metabolite of arginine via arginine decarboxylase (ADC), an arginine pathway distinct from that of the polyamines. We have recently demonstrated the capacity of agmatine to suppress polyamine biosynthesis and to transport in an antizyme-dependent fashion [15]. The induction of antizyme was previously thought to be exclusively in response to intracellular polyamine levels. Agmatine is the only known molecule to date, exclusive of the canonical polyamines, with the capacity to induce antizyme. Agmatine has been previously described to interact with a number of receptors [16-19], and many effects were proposed to be receptor dependent. The induction of antizyme by agmatine, however, was shown to be receptor independent [15]. In accord with the observation of antizyme induction, agmatine administration markedly reduced intracellular polyamine levels and cellular proliferation in a transformed proximal tubule cell line, suggesting a role for agmatine as a tumor suppressor [15].

Although ADC activity is most prevalent in the kidney and the liver [20, 21], agmatine is distributed by the plasma and has been shown to be selectively concentrated in several organs [20, 22]. We have found, in fact, that agmatine was effective at suppressing ODC activity in all immortalized and transformed cell lines examined [15]. To begin to explore the possibility that agmatine is selectively targeted to rapidly proliferating and/or transformed cells, we used the fibroblast-like NIH 3T3 cell line and a more rapidly growing Ras-transformed NIH 3T3 variant (Ras-3T3) as a model system. We observed that the uptake of agmatine by the Ras-3T3 cell line was higher than in the native NIH 3T3 cells. This increased transport capacity for agmatine by Ras-3T3 cells was reflected in their increased sensitivity, over NIH3T3 cells, to agmatine-mediated suppression of proliferation and cell cycle effects (manuscript in preparation).

Agmatine depletion of polyamines can inhibit cell growth [15]. The extent of this effect on proliferation may be limited to the cell’s ability to incorporate agmatine. We hypothesize that agmatine may be selectively targeted to more rapidly proliferating cells, which would further support agmatine as a potential endogenous tumor suppressor. Defining an agmatine transport system is an important aspect of this hypothesis and is currently under investigation.
Besides its capacity to regulate intracellular polyamine levels, agmatine has been ascribed several roles in association with neurotransmitter receptors [16–19]. Agmatine has also been shown to modulate opioid analgesia [23], and possibly has also been shown to modulate opioid analgesia [23], and possibly suppress nitric oxide synthases [25, 26]. Cloning and characterization of a mammalian ADC gene would be an significant step in further understanding the ramifications of this emerging pathway in normal and aberrant physiology.

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