A ROLE FOR ANTIZYME INHIBITOR 2 IN THE BIOSYNTHESIS AND CONTENT OF HISTAMINE AND SEROTONIN IN MOUSE MAST CELLS

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Polyamines (putrescine, spermidine and spermine; PAs) are required for the survival of the majority of living cells. Antizymes and antizyme inhibitors are key regulatory proteins of PA levels by affecting ornithine decarboxylase, the rate-limiting biosynthetic enzyme, and PA uptake. In addition to PA, mast cells (MC) synthesize and store in their granules the biogenically active amines histamine (Hia) and serotonin (5-HT), which are of critical importance for their function. Previously, we have performed several studies in this cell type regarding the interplay between the metabolisms of PAs and Hia and 5-HT. Our results showed that PAs affect Hia synthesis during early stages of IL-3-induced bone marrow cell differentiation into bone marrow derived MCs (BMMCs) and demonstrated that PAs are present in MC secretory granules and are important for granule homeostasis, including Hia storage and 5-HT levels. A few years ago, a novel antizyme inhibitor (AZIN2) was described. In contrast to AZIN1, AZIN2 expression is restricted to a few tissues and cell types including brain, testis and MCs. In MCs, it was recently described that AZIN2 could act as a local regulator of PA biosynthesis in association with the 5-HT granule content and release. At present, our aim is to gain further insight into the role of AZIN2 in the biosynthesis, storage and release of both Hia and 5-HT. In this study, we have generated BMMCs from both wild-type and transgenic mice with severe Azin2 hypomorphism, and have analyzed the content of PAs, Hia and 5-HT, and some elements of their metabolisms. Both PAs and 5-HT levels were reduced in Azin2 hypomorphic BMMCs compared with wild-type controls, whereas the amount of Hia was increased. Accordingly, the level of tryptophan hydroxylase 1 (the key enzyme for 5-HT biosynthesis) was reduced and the amount of enzymatic activity of histidine decarboxylase (the enzyme responsible for histamine biosynthesis) was increased in Azin2 hypomorphic BMMCs. Taken together, our results show evidence that AZIN2 has an important role in the regulation of Hia and 5-HT biosynthesis and storage in MCs.

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