Induction of mast cell apoptosis by Mefloquine

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Among immune defense cells in our body, mast cells are well known for having large amounts of secretory granules. Such granules contain different mediators including numerous active enzymes that are released into extracellular environment upon activation. These cells are tissue resident cells of the innate immune system that play key protective roles against a wide range of parasitic (mainly worms) and bacterial infections as well as snake toxins. However, in addition to their beneficial roles, mast cells and many of their mediators are associated with several disease conditions such as allergic reactions (e.g. food allergies, hypersensitivity disorders of the skin, hay fever and anaphylaxis), asthma, autoimmune disorders and promotion of tumors.

Based on harmful roles of mast cells in allergy-related diseases as well as non-allergic conditions, there is an urgent need to improve strategies that limit their adverse functions. The therapeutic approaches that are available today are mainly helpful for managing the symptoms rather than curing the disease. However, reduction or elimination of mast cells by induction of apoptosis (also known as programmed cell death) has been recently proposed as a novel effective approach for treating not only the symptoms but also the cause of such diseases. Apoptosis is a tightly regulated mechanism of cell death in multicellular organisms. At the end stage of apoptosis, small vesicles called apoptotic bodies are formed which are then taken up by specialized immune cells called phagocytic cells without creating any inflammation.

In this study, the ability of mefloquine, which is an antimalarial drug, to induce mast cell apoptosis through lysosomal damage was examined. Other investigators have previously reported that mefloquine, besides having antimalarial effects, can induce cell death in different cancer cell lines through lysosomal damage. Knowing that mast cells have large amounts of secretory granules that highly resemble lysosomes, we hypothesized that these granules might also get damaged by mefloquine, thus become leaky in response to mefloquine treatment.

In fact, previous studies by our group have revealed for the first time that release of mast cell granule contents induced by lysosomal permeabilizing agants (such as LLME and siramesine) leads to activation of apoptosis and mast cell death. Based on these observations, we tested whether mefloquine can induce cell death in mast cells via a similar mechanism. Indeed, we demonstrate that treatment of mast cells with mefloquine is followed by granule leakage and cell death. Further investigations confirmed that apoptosis is the underlying cause of the observed cell death. In conclusion, these findings suggest mefloquine as a novel future therapeutic candidate for limiting the adverse function of mast cells in disease context.

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