Optimize Peptide Polybia-MP1 as Potential Anticancer Agents

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Polybia-MP1 is a well-known antimicrobial peptide isolated from the venom of a Brazilian wasp named Polybia Paulista. Recent studies suggested that it can inhibit the growth of multidrug-resistant leukemia, prostate, and bladder cancer cells without affecting healthy cells. However, the pharmacological property of Polybia-MP1 still needed to be further improved as it has several drawbacks, which mostly include the high susceptibility to protease and the biological potency only in moderation. While searching for a solution, we found an emerging technology called the "all-hydrocarbon stapling system" that could be a good choice. In a previous study, this chemical strategy dramatically stabilized the helical structure, significantly enhanced trypsin resistance and antimicrobial activity of the stapled analog MP1S. Therefore, in our study, we tried to examine the possibility of this chemical technology in improving anticancer activity. We also created new optimized analogs (MP2S and MP3S) bearing a different stapling system from the one in the reported analog MP1S. Our data suggested that all the stapled analogs were significantly more potent against lung cancer cell A549 whereas displayed a modest increase in hemolytic activity. Overall, we confirm the great potential of "all-hydrocarbon stapling system" in promoting anticancer activity of Polybia-MP1. Moreover, MP3S with the most helical stability and 3.3-fold more potent than the natural version could be a promising compound for developing new anticancer therapeutics that can cope with the drug resistance problem.