Commentary

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Caspase-8 Inhibitor Enhances the Anti-Myeloma Effect of Lenalidomide and Bortezomib

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The protein cereblon (CRBN) is a thalidomide-binding protein [1], and can mediate the anti-myeloma effect of thalidomide and its analogs lenalidomide and pomalidomide [2,3]. We found that the proteasome inhibitor bortezomib could induce the cleavage of CRBN in different myeloma cell lines, but not in HEK293T cells, suggesting that the CRBN cleavage is cell type specific[4]. The cleaved band of CRBN was observed in myeloma cell lines upon 2-10 nM bortezomib treatment for 24 h, indicating that a low concentration of bortezomib could cause the cleavage of CRBN. Subsequent experiments showed that proteasome inhibitors bortezomib and MG-132 induced the cleavage of CRBN, and the drugs tunicamycin, brefeldin A, and cisplatin could not cause the cleavage of CRBN, suggesting that the CRBN cleavage is drugs specific [4].

Our previous study revealed that caspase-8 activation caused the CRBN cleavage[5]. In line with this, we discovered that bortezomib activated the caspase-8, and thus resulted in the CRBN cleavage. Furthermore, the bortezomib-induced CRBN cleavage was also observed in primary myeloma cells of myeloma patient [4]. Considering the crucial role of CRBN in anti-myeloma effect of lenalidomide. Finally, we treated the caspase-8 deficient myeloma cells with lenalidomide and bortezomib, and revealed that the caspase-8 attenuated the anti-myeloma effect of lenalidomide and bortezomib [4,5]. This study suggested that a caspase-8 inhibitor would enhance the anti-myeloma effect of lenalidomide and bortezomib.

Although this study uncovered that activation of caspase-8 would cause the worse lenalidomide-based therapy in myeloma patients, elevation of caspase-8 would increase the apoptosis of cancer cells upon death receptor activation. Therefore, it would benefit the myeloma patients if we could enhance the caspase-8-induced apoptosis and attenuate the caspase-8-mediated anti-proliferative activation of lenalidomide and bortezomib.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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