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Radioprotective and radiomitigative efficacies of CBLB502 are mediated through granulocyte-colony stimulating factor and interleukin 6.

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It has been demonstrated previously that Salmonella flagellin derivative CBLB502 may serve as an excellent radiation countermeasure if administered in a protective regimen. Flagellin/CBLB502-elicited radioprotection required TLR5 and the TLR signaling adaptor MyD88. Radioprotection was, at least in part, mediated via direct effects CBLB502 on cells in bone marrow. It was well documented that flagellin is a particularly potent activator of proinflammatory mediators, mostly cytokines and chemokines, that induce immune cell trafficking and activation, including the recruitment of neutrophils and dendritic cells. It was observed that radiosensitive and radioresistant cells played distinct roles in the innate response to flagellin giving rise to different sets of cytokines.

The purpose of this study was to elucidate the role of granulocyte colony-stimulating factor (G-CSF) and interleukin 6 (IL-6) induced by CBLB502 in protection and mitigation of radiation injury. C57BL/6 mice were injected with different doses of CBLB502 either before (-30 min) or after (+24h) lethal (9.5 Gy) total body irradiation (TBI) and survival over 30 days was monitored. Two routes of administration –intravenous and subcutaneous –were evaluated evaluated for both prophylactic and treatment schedules. The levels of cytokine in serum for both schedules were determined as well.

Here we demonstrated that the levels of G-CSF and IL-6 after CBLB502 administration reflect CBLB502 radioprotective and mitigative efficacy and may serve as biomarkers. The role of these two cytokines was confirmed using neutralizing antibodies during treatment of acute radiation syndrome (ARS) by CBLB502 administration after lethal TBI. Using the approach of generating bone marrow irradiation chimeras we also demonstrated that functional TLR5 expression in both nonhemopoietic (radioresistant) and the hemopoietic (radiosensitive) compartments is necessary to achieve CBLB502 radioprotection.

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