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Hedgehog signaling scenario in the hematopoietic microenvironment of chronic agricultural pesticide induced aplastic bone marrow

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Overactivation of hedgehog signaling has been found to be associated with a wide variety of hematological and nonhematological malignancies including cancer stem cells. However, involvement of the hedgehog signaling system in bone marrow hematopoietic microenvironment during the progression of the bone marrow aplasia is absolutely unknown. In the present work, we have developed an agricultural pesticide formulation (fungicide, organophosphate and pyrethroid) induced bone marrow aplasia mouse model to recapitulate the human aplastic anemia like condition in the laboratory to study the aplastic hematopoietic microenvironment in the light of HH-GLI signaling pathway. Our study has unfolded the fact that chronic pesticide exposure caused downregulation of intrasignaling feedback of PATCH1 and GLI1 by inhibiting the SMO internalization and upregulating downstream negative regulators SU(FU), PKC- δ and β TrCP. Upregulation of negative regulators not only hampers the execution of the hedgehog signaling but also cripples the autocrine-paracrine crosstalk

in between bone marrow primitive compartment and stromal compartment. Simultaneously, individual pesticide versus hedgehog signaling study revealed that hexaconazole disrupted hematopoietic hedgehog signaling activation by inhibiting SMO and facilitating PKC- δ expression. Contrarily, chloropyrifos increased the cytoplasmic sequestration and degradation of GLI1 by upregulating SU(FU) and β TrCP sequentially. Whereas, cypermethrin mediated antagonization of the hedgehog signaling was circumvented by noncanonical activation of GLI1. However, such marrow degenerative condition can be compensated by the recombinant sonic hedgehog. We can conclude that pesticide exposure induced bone marrow aplasia is the direct manifestation of downregulated hedgehog signaling in the bone marrow microenvironment and application of recombinant sonic hedgehog could be a way to improve the overall scenario.

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