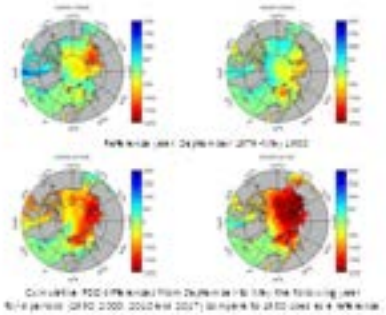
Agricultural pesticide induced bone marrow aplastic anaemia and the hedgehog signaling scenario

Multiple health hazards and fatalities from the widespread use of pesticides have been reported by the WHO. Developing countries primarily dependent on agriculture for their economies such as India, Bangladesh and ailand are especially reliant on these chemicals. Consequentially, public health has been on a decline and there is a lacuna of knowledge about the e ect of pesticide exposure on bone marrow haematopoietic system. e on- eld scenario was mimicked in murine model to explore the consequences of chronic pesticide exposure. 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 βTrCP. 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 βTrCP sequentially. Whereas, cypermethrin mediated antagonization of the hedgehog signaling was circumvented by non-canonical 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.



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