Synopsis of Original Research Paper

Potential involvement of ferroptosis in cell death by rhododendrol

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Rhododendrol is metabolized to rhododendrol quinone by tyrosinase in melanocytes. Reactive oxygen species, such as hydroxyl radical and singlet oxygen, are produced and cause oxidative damage in melanocytes. Recent study has revealed that ferroptosis, a non-apoptotic, iron-dependent cell death, appears to be involved in pathogenesis of a variety of diseases. It is likely that rhododendrol-induced leukomelanodermia is also caused by ferroptosis by means of lipid peroxidation products produced during rhododendrol oxidation in melanocytes. Singlet oxygen also induces feroptosis, and, on the contrary, radical scavenger edaravone effectively suppresses feroptosis caused by cysteine deprivation. Singlet oxygen is commonly produced via photon-mediated energy transfer reaction and also tyrosinase-catalyzed rododendrol metabolism, so that it is likely that ferroptosis is induced by resulted singlet oxygen in melanocytes upon UVB irradiation.

Here we first established a rat monoclonal antibody (FerAb) against Hepa 1-6 cells that had been cultivated in cystine-deprived media. Binding of the resulting antibody increased during advancing ferroptosis which was caused, not only by cystine deprivation but also treatment with xCT inhibitor erastin or GPX4 inhibitor RSL3, although apoptotic cell death induced by a staurosporine treatment had no effect on the binding. Thus, FerAb appears to be the useful tool to detect ferroptosis. When we examined effects of rhododendrol on human melanocyte MNT1 cells, it damaged the cells only at high dose. However, precise analyses of the cells by means of FACS indicated that only less-differentiated cells containing low levels of melanin appeared to die by the rhododendrol treatment. This is similar to the *in vivo* situation, and hence this cell culture system using the MNT1 cells may be ideal model system for rhododendrol-induced melanocyte death.