Involvement of intracellular Fe^{2+} against oxidative stress in CRR cells

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To achieve more effective cancer treatment, we have established and analyzed "clinically relevant radioresistant (CRR) cells" that can survive exposing to 2 Gy/day X-rays for more than 30 days. CRR cells show resistance against hydrogen peroxide (H_2O_2) that is one of the reactive oxygen species. However, the resistant mechanism to H_2O_2 has not been elucidated yet. Therefore, we investigated the involvement of iron ion in the resistant mechanism to H_2O_2 in CRR cells because iron ion has been reported to react with H_2O_2 and produce hydroxyl radical (・OH). ・OH have been shown to react with plasma membrane phospholipid and lead to cell death. Internal Fe^{2+} and ・OH amount were decreased in CRR cells compared with its parental cells. In addition, expression of ferritin, which is iron-binding protein, was increased in CRR cells. No internal H_2O_2 increase and no lipid peroxidation were seen in CRR cells after 50 μM H_2O_2 treatment for 2 hours, whereas internal H_2O_2 uptake and lipid peroxidation was increased after 50 μM H_2O_2 treatment for 2 hours in parental cells. Furthermore, Pretreatment of 10 μM of $FeCl_2$ leads to more cell death after administration of 50 μM H_2O_2 in CRR cells. Administration of phospholipid also led to further cell death after 50 μM H_2O_2 treatment in CRR cells. These results suggest that intracellular Fe^{2+} content is very important against oxidative stress response in CRR cells and control of Fe^{2+} amount may be an effective option for cancer that is resistant to treatment.