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Dissertations-Kurzfassung

Anticancer activities and immunoregulatory properties of a novel mitochondria-targeted antioxidant SkQ1

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ROS is a group of highly reactive molecules containing oxygen and originally considered as harmful byproduct of cellular respiration. However, ROS also regulates various cellular functions by participating in signaling. For immune system, a delicate oxidation-antioxidation balance is essential for regulating the functions of immune cells. Disruption in the redox homeostasis leads to oxidative stress and damages, and subsequently to various diseases including cancer. Many anticancer therapies employ ROS-mediated mechanisms, either through ROS-elevation or through ROS-depletion, to kill cancer cells, and such approaches have shown promising effects.

SkQ1 is a mitochondria-targeted antioxidant which specifically accumulates in mitochondria and has extreme efficiency in scavenging ROS. SkQ1 has shown some anticancer activities *in vivo*. However, the underlying mechanism(s) is unclear. Due to the relation between ROS and immune system, the aim of this study is to investigate whether SkQ1 processes any immunoregulatory properties.

Survival analysis showed that SkQ1 improved the median survival of pancreatic carcinoma bearing mice, implying beneficial effect of SkQ1 against the cancer. Since SkQ1 showed no direct cytotoxic effect against pancreatic cancer cell lines, we speculated that the improved survival might be resulted from the influence of SkQ1 on the immune system.

In healthy mice, SkQ1 treatment decreased the percentage of naïve T cells while increased the percentage of memory T cells. No difference was detected for Tregs, NK and NKT cells. SkQ1 treatment also increased the percentage of pDCs while reduced the percentage of granulocytes.

In *ex vivo* murine splenocyte culture, SkQ1 treatment resulted in a higher frequency of $CD4^+$ T cells and $CD8^+$ T cells, while a lower percentage of B cells.

In tumor bearing mice, all SkQ1 treatments inhibited tumor growth. Metastasis was significantly inhibited in mice with SkQ1 pretreatment, compared with those received no pretreatment.

Also in tumor bearing mice, SkQ1 pretreatment had the highest percentage of $CD8^+$ T_{EM} cells and T_{CM} cells, while the lowest naïve $CD8^+$ T cells in spleen and in tumor. SkQ1 had no effect on Tregs, NK cells and MDSCs. But for NKT cells, all SkQ1 treatment schemes decreased the NKT cell frequency in spleen and in tumor. Like in healthy mice, SkQ1 pretreatment significantly increased the percentage and maturation state of pDCs in spleen and in tumor.

For human peripheral T cells, SkQ1 treatment showed no effect on the percentage of subpopulations. No difference in the expression of activation markers and regulatory molecules was detected. This implies the absence of direct effect of SkQ1 on T cells.

In conclusion, our study shows that SkQ1 has potential anticancer activities in inhibiting pancreatic cancer growth and metastasis, with SkQ1 pretreatment show the most obvious inhibition. In addition, we find that SkQ1 possesses certain immunoregulatory properties *in vivo*. The effects of SkQ1 on various immune cell types may be responsible for the improved survival, tumor growth and metastasis. For further understanding the relation between the effect of SkQ1 on immune system and the anticancer activities, more studies are still needed.