**Autocrine and paracrine LIF signals to collaborate Sorafenib-resistance in Hepatocellular Carcinoma and effects of Kanglaite Injection**

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**Background and aims.** Sorafenib (SFN) is the first-line medicine for advanced hepatocellular carcinoma (HCC). However, Sorafenib (SFN) resistanc e is a main challenge of therapeutic efficacy, and the mechanisms have not been fully clarified1,2. The purpose of this study was to investigate the therapeutic potential and mechanism of action of LIF in modulating the microenvironment of SFN resistance as well as Kanglaite Injection (KLTI) in ameliorating SFN resistance in HCC and to guide future research directions for drug combination for HCC.

**Methods.** Established SFN-resistance HCC cell line was used to study the relationship between resistance and immunosuppression in HCC-tumor microenvironment (TME). In vivo macrophage and natural killer (NK) cell depletion were achieved by clodronate liposomes (CL) and anti-NK1.1. In vitro multiple cell co-culture systems were used to determine the effects of KLTI on SFN-resistant. Likewise, flow cytometry, qRT-PCR, Western blot, and immunohistochemistry analysis were performed for further mechanistic investigation.

**Results.** Tumor associated-macrophages (TAMs) and NK cells mediated SFN-resistance in murine HCC. In the case of SFN resistance, the paracrine-leukemia inhibitory factor (LIF) by M2-like TAMs increased and potently suppressed NK cell proliferation and cytotoxicity, which finally inducing NK exhaustion and malignancy of HCC metastasis. Meanwhile, SFN resistance led to the increased autocrine-LIF of tumor cells, and further promoted the protective autophagy and activation of the acquired drug-resistant pathway PI3K/Akt/mTOR. KLTI could ameliorate the resistance of tumor immune microenvironment (TIME) and enhance the sensitivity of HCC to SFN by regulating LIF and macrophage-NK cell interaction.



**Figure 1.** SFN-R promotes M2-like macrophage polarization and forms an autocrine LIF/IDO1 loop to inhibit NK cell cytotoxicity and induce immune escape, while KLTI targets LIF to improve the resistance-TME and enhance SFN’s anti-tumor activity.

**Conclusion.** Our findings verify the therapeutic effects of targeting LIF in SFN-resistance, uncover the potential mechanism for the increased sensitivity to SFN and sought to elucidate how this intervention might contribute to overcoming SFN resistance. KLTI is a promising immunomodulatory drug by regulating LIF and macrophage-NK cell interaction, which could be a potential combination partner for HCC treatment.

**References:**

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