Sorafenib enhances mast cells maturation and degranulation in human skin

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Introduction

Sorafenib (Nexavar®) is a multi-kinase inhibitor for treating hepatocellular and renal cell carcinomas by targeting various types of receptors and signaling molecules, including vascular endothelial growth factor receptors, platelet-derived growth factor receptor, and Raf-1.¹⁾ Sorafenib is regarded as one of the most powerful options for treating these advanced cancers.²⁾ Sorafenib has been reported to cause diverse cutaneous reactions including itch.³⁾ However, the mechanism has not been well-investigated.

Hypothesis

Mast cells (MCs) could be related the mechanism of sorafenib-induced cutaneous adverse reactions because MCs are reported to be associated with various types of skin diseases including drug eruption and pruritus.⁴⁾

Method

To investigate the mechanism of sorafenib-induced adverse reactions, we focus on MCs by using human skin organ culture system⁵⁾ and skin samples from patients with drug eruption by sorafenib.

Fig.1 Sorafenib (1 μM) increased the number of skin-type MCs.

Fig.3 Sorafenib may stimulate skin-type MC maturation *in situ*.

Fig.4 Sorafenib increased stem cell factor (SCF) expression.

Fig.5. The co-administration of SCF neutralizing antibody diminished the increase in MC number by sorafenib.

Fig.2 Sorafenib induced MC degranulation *in situ*.

• Sorafenib did not affect MC proliferation and apoptosis.
• MC number *in situ* is controlled by their proliferation, apoptosis, and maturation.

This suggests that sorafenib stimulated MC maturation from resident precursor cells.

Sorafenib increased MC number and degranulation *in situ*.

Fig.6 Compensatory upregulation of PI3K signaling was induced by the inhibition of MAPK signaling by sorafenib.

• PI3K inhibitor, wortmannin abrogated the increased number of MCs by sorafenib.

• Sorafenib significantly increased Akt (PI3K) immunoreactivity within the c-Kit+ MCs.

• The increased MCs induced by sorafenib may be controlled via the PI3K signaling pathway.

This suggests that the compensatory upregulation of PI3K-signaling was induced by the inhibition of MAP kinase signaling by sorafenib.

Fig.7 Sorafenib increased the number of tryptase MCs and degranulation and SCF in the skin lesions of patients treated within three weeks of sorafenib.

Age	Sex	Disease treated with Sorafenib	Site of skin biopsy	Period from administration of Sorafenib to skin biopsy	Types of drug eruption	Patient's skin sensation
61	M	RCC	knee	7 days	EM type	itch
51	M	RCC	hand	7 days	hand-foot reaction	painful
22	F	HCC	upper arm	10 days	EM type, Alopecia	itch
63	F	RCC	forearm	11 days	EM type	itch
68	F	HCC	chest	14 days	EM type	painful
85	F	RCC	upper arm	14 days	EM type	itch
65	F	TC	upper arm	21 days	Maculopapular type	itch
56	M	HCC	femur	47 days	EM type, Pustular drug eruption	itch

When we investigated MCs biology within the skin samples from the patients with sorafenib induced drug eruptions, the number of degranulated and total MCs and SCF expression was significantly increased.

Summary & Conclusion

1. Sorafenib increased mast cell number and stimulates mast cell maturation and induces degranulation.
2. Sorafenib also increases SCF expression.
3. The effect of sorafenib on mast cell maturation is mediated via PI3K signaling.
4. PI3K mediated signaling or SCF could be a new target for sorafenib-induced itch.

Sorafenib induces itch via activation of degranulation and maturation of skin-type MCs.

This activation is related to PI3K signaling and SCF production, which could be new targets for treating sorafenib-induced cutaneous reaction including itch.

Reference

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