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CKD-516, a novel oral VDA, enhances anti-cancer activity of anti-PD-1 antibody in SMAD4-deficient colon cancer model

Soo Jin Kim[1)], Hark Kyun Kim[2)], Eungchang Lee[3)], Inhak Choi[3)], Keun Ho Ryu[1)], Chung Il Hong[1)]

CKD Research center, 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 16995, Korea[1)]
National Cancer Center, 323 Ilsan-ro, Goyang-si, Gyeonggi-do 10408, Korea[2)]
Inje University College of Medicine, Bokji-ro 75, Busanjin-gu, Busan 47392, Korea[3)]

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Abstract

CKD-516 is a potent vascular disrupting agent (VDA), selectively acting on tumor vessels. A clinical study of CKD-516 combined with irinotecan is undergoing in colorectal cancer.

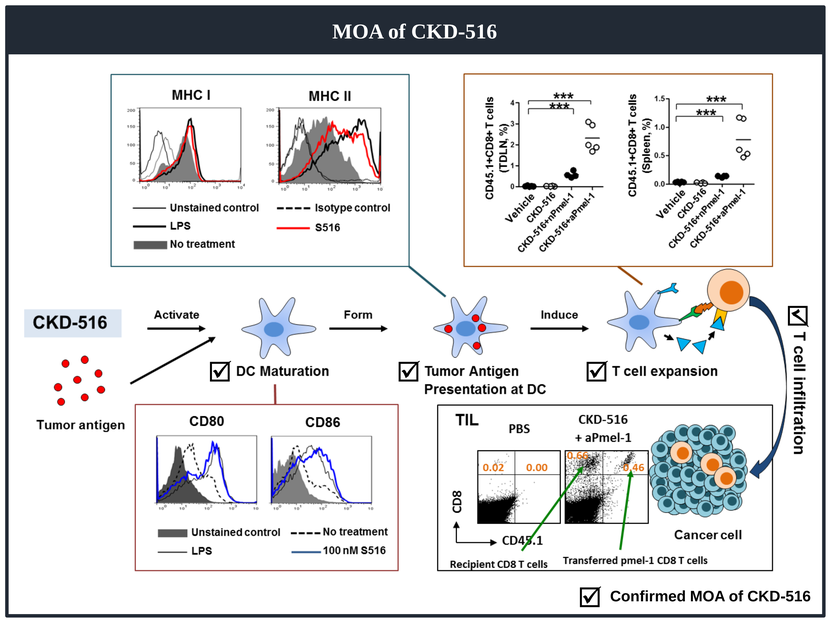
There have been exponential gains in immune-oncology (I-O) in recent times through the development of immune checkpoint inhibitors (ICIs). ICIs demonstrated durable response and some patients achieved disease control for several years. However, there are still critical unmet medical needs for the combination therapies due to limited response rate of ICIs.

The first step of the cancer-immunity cycle is dendritic cells (DCs) maturation which is necessary for the anti-cancer immunity. It is well known that mature DCs play critical roles in priming immune responses in cancer patients. We found that CKD-516 is able to induce DC maturation through Rho signaling pathway in DCs.

A tumor suppressor gene, SMAD4 is associated with several cancers including stomach cancer, colorectal cancer (CRC), and pancreas cancer.[1-2)] The loss of SMAD4 is a poor prognostic biomarker in these cancer types and its mutation is related to poor clinical outcome for immunotherapy as well as chemotherapy.[3)] A SMAD4-deficient mouse colorectal cancer cell line (3349LM) was primary cultured from a spontaneous intestinal adenocarcinoma formed in a *Villin-Cre;Smad4(F/F);Trp53(F/F)* mouse. SMAD4 loss is well known to cause drug resistance to chemotherapy and immunotherapy. CKD-516 showed a synergistic effect with anti-PD-1 antibody in both of MC38 and 3349LM syngeneic model. In addition, 3349LM is also a MSS type cancer. Thus, CKD-516 displayed a therapeutic potential for cancer patients responsive and/or unresponsive to current immunotherapies.

In summary, CKD-516 is a novel VDA with immune boosting effect. In both immunogenic cancer and non-immunogenic cancer model, CKD-516 has shown synergistic effects in combination with PD-1 antibody. Therefore, these data suggest that CKD-516 potentiates the anti-cancer activity of immunotherapy.

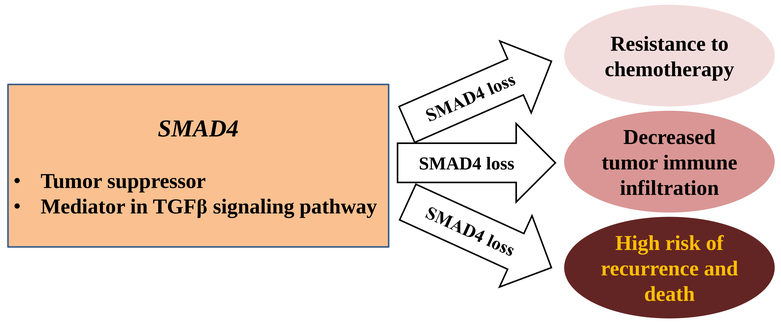
MOA of CKD-516



Introduction

◈ ***SMAD4 loss in colorectal cancer***

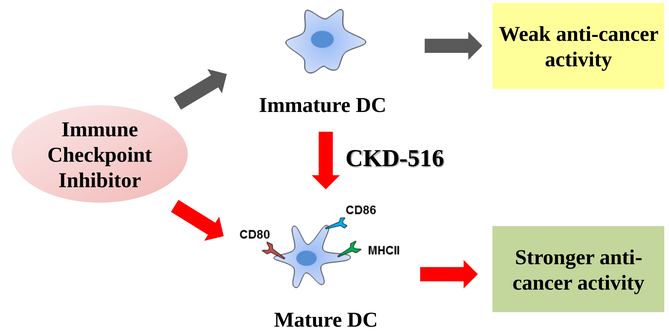
TGFβ signaling pathway plays important roles in many biological processes, including cell growth, differentiation, apoptosis, migration, as well as cancer initiation and progression. SMAD4, which serves as the central mediator of TGFβ signaling[4)], is specifically inactivated in 10~15% of colorectal cancer. SMAD4 loss is a prognostic marker of worse clinical outcome, resistance to chemotherapy, and decreased immune cell infiltration in CRC.[3)]



◈ ***DC maturation in I-O therapy***

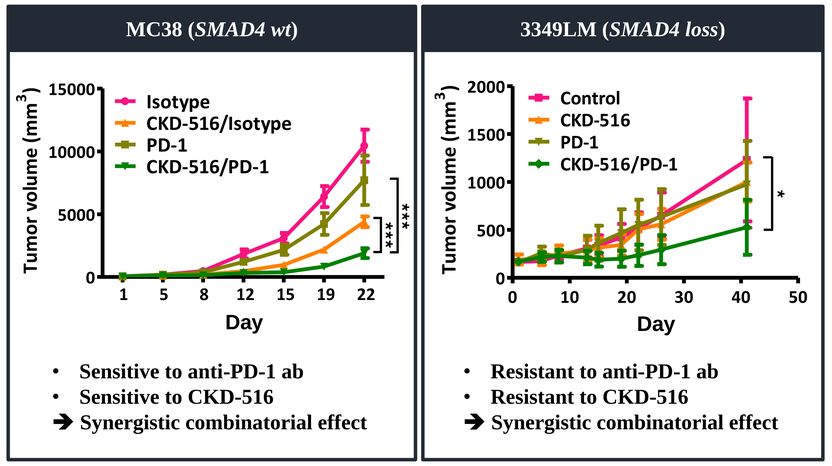
Mature DCs play key roles in priming robust immune responses in tumor-bearing hosts. Importantly, tumors may prevent the generation of sustained anti-cancer immunity by inducing DC dysfunction through a variety of mechanisms.[5-6)]

CKD-516 is a potent inducer of DC maturation. Therefore, CKD-516 should increase the anti-cancer activity by overcoming resistance to immunotherapy.

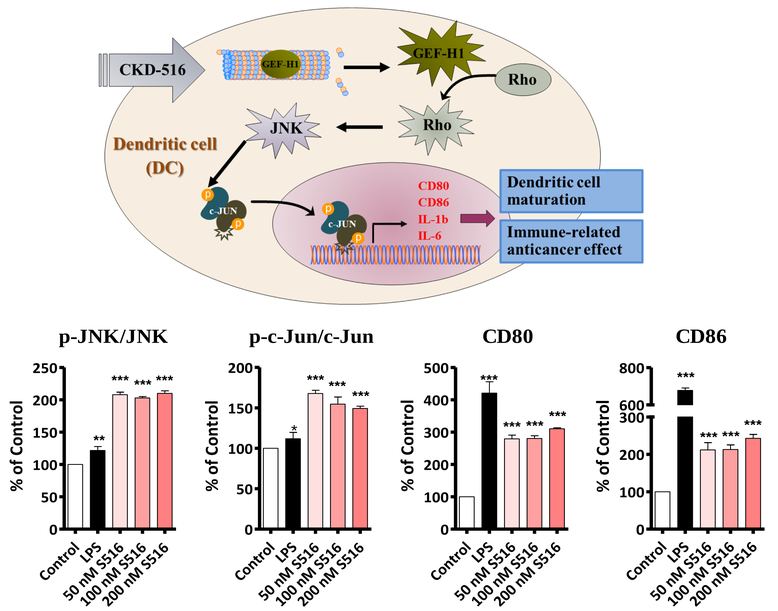


Result

◈ ***Anti-PD-1 antibody combination in mouse syngeneic models***



◈ ***DC maturation via CKD-516 (proposed mechanism)***



Conclusion

Our current work has demonstrated that CKD-516 directly induced DC maturation. In addition, CKD-516 showed synergistic effects upon being combined with ICI in SMAD4 deficient model (non-immunogenic), as well as MC38 model (immunogenic). Therefore, we suggest that CKD-516 provide clinical benefits for both types of patients.

C57BL/6 mouse DCs were used for the experiments. DCs were incubated with the indicated concentration of S516. Activations of JNK and c-Jun were detected by western blotting, and expressions of CD80 and CD86 were detected by real-time PCR.

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3) Clin Cancer Res.(2019) 25(6):1948-56
4) Int J Biol Sci. (2018) 14(2) : 111-23
5) Expert Opin. Biol. Ther. (2002) 2(1):35-43
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