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Commentary

The Clinical Potential of IL-12/IL-35 in Treating Chemotherapy Drug-induced Cardiac Injury

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Chemotherapy is a key strategy for the treatment of various cancers. However, the chemotherapy drug-induced organ injury greatly limited chemotherapy application in clinic [1]. Among the organ injuries caused by chemotherapy drugs, cardiac injury serves as one of the most serious clinical complications [2]. In clinic, a number of chemotherapy drugs including doxorubicin, cisplatin, daunorubicin, paclitaxel, and fluorouracil could result in cardiac injury, even heart failure. In the past decades, although cardiologists and researchers tried to develop effective therapies against chemotherapy drug-induced cardiac injury, the outcome is still disappointing. In the present study in *EBioMedicine*, Ye et al. reported that deletion of interleukin (IL)-12p35 aggravated doxorubicin-induced cardiac injury, while application of IL-12 or IL-35 remarkably attenuated such an injury [3], suggesting a clinical potential of recombinant IL-12 (rIL-12) and rIL-35 for the prevention and treatment of chemotherapy drug-induced cardiac injury.

Actually, both IL-12 and IL-35 belong to IL-12 family and share the same subunit of IL-12p35 [4]. In previous studies, diverse roles of IL-12 in modulating the inflammatory response were documented. IL-12 was reported to promote atherosclerosis via augmenting inflammation [5,6], however, IL-35 could ameliorate the atherosclerotic lesion via an anti-inflammatory mechanism [7]. Interestingly, recent studies provided solid evidence showing that IL-12p35 deletion could promote inflammation to aggravate cardiac fibrosis, indicating a potential role of IL-12p35 in antagonizing chronic cardiac injury associated with the inflammation [8]. However, whether IL-12p35 plays a role in the pathogenesis of chemotherapy drug-induced cardiac injury is unclear. In this research, Ye et al. found that systemic deletion of IL-12p35 aggravated doxorubicin-induced cardiac injury [3]. Furthermore, application of recombinant proteins of IL-12 or IL-35 strikingly ameliorated chemotherapy drug-induced cardiac injury [3]. This important study provided the evidence for the first time showing the beneficial role of IL-12 and IL-35 in protecting against cardiac injury caused by chemotherapy drug doxorubicin possibly through the blockade of inflammation, oxidative stress, apoptosis, and abnormal autophagic response.

Although this report revealed the important role of IL-12p35 in the pathogenesis of chemotherapy drug doxorubicin-induced cardiac injury and suggested a potent potential of IL-12 and IL-35 for treating such a side effect, this research still has some weaknesses that need to be improved in the future studies. First, as shown by the provided data, the invalidation of IL-12p35 or the treatment of IL-12 and IL-35 affected the inflammation, oxidative stress, apoptosis, and autophagic response. However, all these phenomena could be indirect responses and could affect each other. The exact mechanisms of IL-12 and IL-35 in attenuating doxorubicin-induced cardiac injury are still elusive. In fact, for any clinical intervention, it is definitely important to understand the mechanisms contributing to the effectiveness of the therapy. Thus, an intervention on the inflammatory pathways, oxidative stress, apoptosis, or autophagy in IL-12p35-deleted or IL-12- and IL-35-treated animals is needed to identify the possible mechanisms mediating the protective role of IL-12/IL-35 against cardiac injury caused by doxorubicin. Second, application of IL-12 or IL-35 showed significant and comparable amelioration of cardiac injury. However, an additional treatment group with a combination of IL-12 and IL-35 could help to understand an additive effect in this disease model. Third, as mentioned above, a number of chemotherapy drugs like doxorubicin, cisplatin, daunorubicin, paclitaxel, and fluorouracil are cardiotoxic with diverse pathogenic mechanisms. Therefore, it is worthwhile to know that whether the recombinant IL-12 or IL-35 also protect the heart from the injuries caused by other chemotherapy drugs. Forth, it is well established that inflammatory cells, myocytes, and vascular cells all could play similar or distinct roles during the cardiac injury. In this study, global IL-12p35 KO mice and systemic application of IL-12 or IL-35 were employed, which could not define the cell-specific roles of IL-12p35, IL-12, and IL-35 in doxorubicin-induced cardiac injury. In the future, a cell-specific deletion or overexpression of IL-12p35 in animals challenged with chemotherapy drugs are required to clarify this issue. Fifth, as mentioned in the study, IL-12 and IL-35 could play anti-inflammatory and pro-inflammatory roles under different pathological conditions. For example, IL-12 may play a detrimental role in atherosclerosis possibly via promoting the inflammation [5,6]. Thus, to test the efficacy of IL-12 in atherosclerotic animals (like APOE−/− or LDL−/− KO mice with western diet) with chemotherapy drug treatment could help to understand the safety and effectiveness of IL-12 in treating cancer patients with atherosclerosis. Sixth, for the experiment design, the animals were

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pretreated with recombinant Il-12 or IL-35 before the chemotherapy drug treatment. It is known that only some of the patients with chemotherapy will develop obvious cardiac injury and need clinical intervention. Thus, the effect of a post treatment of IL-12 and IL-35 on chemotherapy drug cardiotoxicity should be evaluated.

In summary, employing the IL-12p35 KO mice and recombinant IL-12 and IL-35, the authors reported a beneficial role of IL-12p35 gene in antagonizing doxorubicin cardiotoxicity. These findings also suggested a translational potential of IL-12 and IL-35 for the clinical treatment of chemotherapy drug-induced cardiac injury.

Disclosure

The author declared no conflicts of interest.

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