EBioMedicine 35 (2018) 4–5

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

The clinical potential of IL-12/IL-35 in treating chemotherapy drug-induced cardiac injury – Authors' reply

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Doxorubicin (DOX) is an important chemotherapy drug that can be used in a variety of chemotherapy regimens for cancer patients, but it can lead to serious clinical complications, especially heart damage. In our recent paper, we found that deletion of interleukin (IL)-12p35 (deletion of the shared subunits of IL-12 and IL-35) aggravated DOX-induced cardiac injury and deteriorated cardiac function, while supplementation with exogenous IL-12/IL-35 significantly attenuated the cardiac injury [1]. In his commentary on our paper, Dr. Jia exhibited profound understanding of the role of chemotherapy drugs in myocardial injury, systematically summarized our articles and pointed out some true shortcomings. Dr. Jia also suggested that IL-12/IL-35 has potential clinical value for the treatment of cardiac injury induced by clinical chemotherapy drugs [2]. In summary, we thank Dr. Jia for his professional comments and completely agree that the limitations he raised do exist in our paper. Now, we simply respond to the prospect that IL-12/IL-35 could protect against chemotherapy-induced cardiac injury in the clinic.

The interleukins (ILs) were uniformly named at the second international symposium on lymphocytes in 1979. Thus far, 40 ILs have been discovered and are divided into the IL-1, IL-6, IL-10, IL-12, and IL-17 families according to their biological functions. At first, ILs were thought to have a single function, while the complexity of ILs was gradually recognized with further research. IL-10 and IL-22, two important members of the IL-10 family, were found to play different or even completely opposite roles in previous studies. IL-10 was successively observed to decrease and increase blood pressure in a mouse hypertension model induced by angiotensin II (Ang II) and Ang II with high salt. Surprisingly, another study reported that IL-10 did not affect blood pressure, although it alleviated Ang II-induced vascular dysfunction [3–5]. In studies on IL-22, both pathogenic and protective roles of IL-22 have been found in atherosclerosis and myocarditis, respectively [6,7]. Based on the above studies, the effects of ILs depend on the body environment in which they are found. In fact, this phenomenon has also been observed for IL-12 and T regulatory cells (Treg, one of the most important sources of IL-35) [8,9]. The environment and mechanisms related to cardiac injury induced by other chemotherapy drugs, such as actinomycin, bleomycin, cisplatin, daunorubicin, paclitaxel, and fluorouracil, are also different. Due to drug resistance, toxic/side effects and curative effects, clinical cancer patients are often treated with multiple drugs in combination with chemotherapy. The combination of chemotherapy drugs in the clinic further complicates the body environment. As mentioned above, it is not known whether IL-12/IL-35 can protect against cardiac injury induced by different chemotherapy regimens. Therefore, many further studies on the roles of IL-12/IL-35 in different chemotherapy regimens are required.

In addition to the biological environment of the body, dose is another important factor affecting the biological effects of ILs. IL-37 is considered to be the only anti-inflammatory agent in the IL-1 super family, and it is expressed in humans, but not in mice [10]. Early studies reported that IL-37 binds to the alpha chain of the IL-18 receptor (IL-18Rα); it was regarded as an antagonist of IL-18, playing an anti-inflammatory role via inhibition of the biological effects of IL-18. Because of the very low affinity of IL-37 and IL-18Rα, some researchers increased the dose of IL-37 and found that only low concentrations of IL-37 effectively inhibited proinflammatory cytokine production in vitro, while high concentrations of IL-37 initiated a strong proinflammatory signal [10]. In previous studies on acute DOX-induced cardiac injury, pretreatment with high doses of drugs was usually performed three to five days before DOX treatment; therefore, based on previous studies about IL-12 and IL-35, some wild-type mice were intraperitoneally injected with 5 μg of recombinant mouse IL-12 or 5 μg of recombinant mouse IL-35 before

DOIs of original article: https://doi.org/10.1016/j.ebiom.2018.06.009, https://doi.org/10.1016/j.ebiom.2018.08.018.

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https://doi.org/10.1016/j.ebiom.2018.08.049

three days of DOX treatment. Our results showed that high doses of both rIL-12 and rIL-35 almost completely reversed DOX-induced cardiac injury. Unfortunately, we did not measure the serum IL-12 and IL-35 levels after treatment and therefore do not know the degree to which serum IL-12 and IL-35 increased. The results suggested that lower or higher doses of IL-12 and IL-35 probably would not affect DOX-induced cardiac injury and may even aggravate the cardiac injury, similar to IL-37. Therefore, investigating the effect of different IL-12/IL-35 concentrations on different chemotherapy-induced cardiac injuries may be very interesting and meaningful.

In summary, our research indicates that both IL-12 and IL-35 have protective effects against myocardial toxicity induced by DOX and provides some ideas for the prevention and treatment of myocardial injury mediated by clinical chemotherapy drugs. Much research must still be done before IL-12 and IL-35 can be used clinically to protect against the cardiotoxicity induced by chemotherapy drugs.

Conflicts of interest

The author declared no conflicts of interest.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 81770472, 81460081, 81460061 and 81760051).

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