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The flip side of doxorubicin

Inflammatory and tumor promoting cytokines

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Cardiac toxicity is a major dose-limiting factor for the anthracycline drug doxorubicin. The reasons why doxorubicin causes heart damage are not fully understood, and the manuscript by Wong et al. postulates that inflammatory cytokines released from macrophages or other cell types may play a significant role in the damage process in response to doxorubicin and possibly other chemotherapeutic agents.[1] Expression of many cytokines requires activation of both the p38 MAPK and JNK pathways and, additionally, doxorubicin toxicity can be blocked by combined inhibition of both pathways.[2,3] The MAP3K responsible for doxorubicin-induced p38 MAPK and JNK activation in keratinocytes was previously shown by these authors to be ZAK.[4] ZAK is of note because it can be targeted by FDA approved agents such as nilotinib and sorafenib.[4-7]

In the present manuscript the authors show in vitro that bone marrow derived macrophages from ZAK$^{-/-}$ mice lack activation of p38 MAPK or JNK in response to doxorubicin. A lack of ZAK signaling through p38 MAPK and JNK was then shown to result in lower induction of cytokine expression e.g., IL-1, IL-6. In vivo the authors show that doxorubicin treatment stimulates liver Kupfer cell expression of inflammatory cytokines; an effect that is blocked by nilotinib. Collectively the data argue that combined inhibition of p38 MAPK and JNK, or selective inhibition of ZAK may be a useful approach to reduce inflammation after doxorubicin therapy.

The authors noted the hypothetical possibility that if doxorubicin-induced activation of p38 MAPK/JNK is reduced by ZAK inhibitory drugs, it could imply that the level of tumor cell killing by doxorubicin in combination with such inhibitors will also be reduced. Fortunately, it has been shown that nilotinib synergizes with doxorubicin to kill sarcoma cells, and that in hepatocellular carcinoma sorafenib and doxorubicin extend overall and progression-free survival compared with single agent doxorubicin.[8,9] A criticism of the present study is that the authors did not perform any in vivo studies examining cardiac function in wild-type and ZAK$^{-/-}$ mice treated with doxorubicin, which would appear to be essential to prove their hypothesis. The reconstitution of ZAK$^{-/-}$ mouse bone marrow with wild-type progenitors would confirm the need for macrophage inflammatory mediator effects on the heart. The present studies also did not examine cardiac muscle biology in wild-type and ZAK$^{-/-}$ littermates which would have confirmed or refuted whether ZAK regulates MAPK signaling in cardiac muscle as it does in macrophages or keratinocytes.

The increase in IL-6 plasma concentrations following doxorubicin treatment is reminiscent of other studies showing that ionizing radiation can cause the release of growth factors into the media/patient plasma e.g., TGFα.[10] IL-6, like TGFα, is a potent mediator of tumor cell growth and the fact that doxorubicin increases plasma IL-6 levels will be counter-productive to achieving a PR or CR in a patient using this drug, particularly a liver cancer patient.[11] Radiation-induced release of TGFα into the plasma will also be counter-productive to therapeutic control. Thus not only may

doxorubicin and sorafenib prolong patient survival, they may also prevent tumor regrowth by blocking IL-6 production.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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