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Letter to the Editor

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LEVESQUE ET AL.

Macrophages Driving Heterotopic Ossification: Convergence of Genetically-Driven and Trauma-Driven Mechanisms[1]

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To the Editor:

We read with great interest the recent article in the *Journal of Bone and Mineral Research* by Convente and colleagues, "Depletion of mast cells and macrophages impairs heterotopic ossification in an *Acvr1*^{R206H} mouse model of fibrodysplasia ossificans progressive."[1] This article reports that muscle injury caused by intramuscular injection of cardiotoxin from Naja mossambica mossambica venom into the *Acvr1*^{R206H} mouse causes the development of heterotopic ossifications (HO) at the injury site. They demonstrated exacerbated macrophage and mast cell accumulation in *Acvr1*^{R206H} mice and showed that depletion of macrophages in vivo with clodronate-loaded liposomes, genetic impairment of mast cells, or a combination of both approaches substantially reduced the volume of HO. The authors conclude that the immune system, particularly macrophages and mast cells, are major contributors to the initiation and development of HO in fibrodysplasia ossificans progressiva (FOP).

This finding of macrophage involvement in the development of HO in FOP is wholly consistent with our previously published work using identical methodology to show that macrophages mediate the development of HO in wild-type mice with spinal cord injury (SCI).[2] In that work, we showed that the combination of SCI with intramuscular injection of cardiotoxin from Naja mossambica mossambica venom causes development of neurogenic HO in wild-type mice. The development of HO in SCI mice recapitulated the clinical features of neurogenic HO in patients with SCI or traumatic brain injury. We also showed that concomitant depletion of macrophages in vivo, using clodronate-loaded liposomes, dramatically reduced the volume of HO in this model of neurogenic HO after SCI.[2]

Convente and colleagues suggest that Substance P, as a neuroinflammatory modulator, may be a major molecular driver of HO. We reported significantly elevated Substance P in serum of patients with neurogenic HO, but that Substance P antagonism was modestly protective in the neurogenic HO mouse model.[2] We concluded that macrophages are key drivers of neurogenic HO in this model.

The role of macrophages in promoting bone formation in HO, both in our model of trauma-induced HO and in Convente and colleagues' *Acvr1* mutant model of HO in FOP,[1] is consistent with our previously published work showing a key role of macrophages in the maintenance of functional osteoblasts, bone formation, and bone repair.[3–6] We have now identified that the range of cytokines induced in macrophages by cardiotoxin injection includes oncostatin M, and secretion of oncostatin M by inflammatory monocytes and macrophages infiltrating the injured muscle is a key driver of HO development and formation of heterotopic hematopoietic stem cell niches in humans and mice with SCI.[7]

In conclusion, we wish to highlight a point that seems to have been overlooked by Convente and colleagues, which is that even though HO development in these two clinically distinct situations (genetically-driven FOP versus trauma-driven neurogenic HO) might be expected to have distinct mechanisms, the use of overlapping methods to interrogate these two models revealed that cytokine production by macrophages is a common underlying cause and thus represents a potential therapeutic strategy for both conditions.

Disclosures

All authors state that they have no conflicts of interest.

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