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Refers to:

The semaphorin 4A–neuropilin 1 axis alleviates kidney ischemia reperfusion injury by promoting the stability and function of regulatory T cells.
Junnan Xu, Xiubin Li, Qing Yuan, Chenfeng Wang, Liang Xu, Xing Wei, Haitao Liu, Bo Yu, Zhekun An, Yuanyu Zhao, Xiang Li, Xu Zhang, Xin Ma, Ming Cai
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We read with great interest the article by Xu et al. recently published in Kidney International[1]. This study reported that Sema4A systemic delivery could help recruit Neuropilin-1 (Nrp1)- positive regulatory T cells (Tregs) to the kidney and alleviate Ischemia Reperfusion Injury (IRI). These encouraging results need to be reconciled with previous studies by Xia and colleagues[2] who investigated the respective contribution to IRI of Semaphorins and their receptors Plexins[3]. These authors did not find changes in either kidney function or kidney damage in PlexinB2-deficient mice 48 hours post IRI. Furthermore they could not detect renal defects in Sema4A-, Sema4B-, Sema4C-, Sema4D-, and Sema4G-deficient mice 7 days post injury. Solely the analysis of triple-knockout mice lacking Sema4B/Sema4D/Sema4G uncovered a role for the class-4 Semaphorin family in kidney repair. While this work emphasised the level of redundancy among these proteins, it also undermined the potential role played by Sema4A alone in the development of IRI.

Another point that deserves special attention is the potential role of circulating Sema4A. Class-4 semaphorins including Sema4A[4] can be released from the cell membrane by proteolytic cleavage and be secreted, then using Neuropilins as their receptors and Plexins as co-receptors[3]. Whether secreted Sema4A could help recruit Nrp1-positive Tregs to the damaged kidney is a possibility, although questionable. Indeed, no increase in Sema4A serum concentration in mice following IRI (supplemental Fig10) and in patients who underwent partial nephrectomy (Supplemental Fig13) were reported by Xu *et al.*[1].

Overall, Xu and colleagues described a rather efficient, albeit artificial, way to overcome IRI and provided convincing data for the implication of the Sema4A-Nrp1 axis. However, their findings are to be pondered in the physiological context of AKI where Sema4a is likely to have no effect in IRI development.

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