We have read the article with interest by Zhuang and colleagues (1) on the combination of IL1R antagonist and gemcitabine in gemcitabine-resistant pancreatic ductal adenocarcinoma (PDAC). The article showed that gemcitabine-induced NF-κB and ERK activation in gemcitabine-resistant PDAC cells can be reversed by anakinra, an FDA-approved IL1R antagonist. However, there are still some key points that should be discussed with more details.

The mutational activity of KRAS has been detected in 85% to 90% of PDAC and 70% of KRAS-mutant PDAC with NF-κB activation. Mutations were found in the second base of codon 12 of KRAS in almost all pancreatic cancer cell lines, except Hs766T and BxPC-3 (2). However, the sensitivity of gemcitabine was not consistent with the mutation of KRAS, both CFPAC-1 and BxPC-1 are sensitive to gemcitabine. So NF-κB signal pathway, as a key downstream of KRAS, might be the critical point.

As demonstrated by the authors, gemcitabine-resistant pancreatic cancer cell lines like AsPC-1 showed activation of NF-κB after the use of gemcitabine, which was considered as a pivotal mechanism of gemcitabine resistance. But unfortunately, previous studies demonstrate controversial opinions on the correlation between the activation of NF-κB and gemcitabine resistance in PDAC. In the study by Pan and colleagues (3), the authors found that NF-κB activity did not correlate with sensitivity to gemcitabine, and gemcitabine treatment did not activate NF-κB either in vitro or in vivo both in gemcitabine-sensitive/resistant pancreatic cancer cell lines. Our group also found that gemcitabine could reduce the activation of NF-κB both in BxPC-3/CFPAC-1 (gemcitabine sensitive) and AsPC-1/PANC-1 (gemcitabine resistant) cell lines. What is more, gemcitabine could not induce NF-κB activation in BxPC-3/GEM cell line in some studies (4), which means that NF-κB activation was not a general result after gemcitabine treatment in different gemcitabine-resistant cell lines, even in the same pancreatic cancer cell line. All the results indicated that NF-κB activation may not be a mechanism of gemcitabine resistance in PDAC, and further evidence is required.

According to previous research, Ling and colleagues (5) revealed that KRASG12D-induced IL1α activated NF-κB and its target genes IL1α and p62 to initiate IL1α/p62 feedback loop, which may be an important mechanism between KRAS mutation and NF-κB activation in the development of PDAC.

In conclusion, we congratulate Zhuang and colleagues: IL1α may be a useful therapeutic target for a subset of pancreatic cancer, but we believe that its mechanism of reversing gemcitabine resistance remains controversial.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Letter to the Editor

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