Scientific summary (Scientific report)

The scientific objectives of our project were to identify which BCL-2 family of proteins are responsible for maintaining neutrophil survival in joints during inflammatory disease. These proteins either promote death or survival, with the expression levels and interactions between these proteins determining how long cells live before they die and are replaced by new cells. There are five known BCL-2 survival proteins: BCL-2, BCL-XL, BCL-W, MCL-1 and A1. Furthermore, we sought to ascertain if therapeutic targeting of these proteins could selectively kill inflammatory neutrophils in joints, without affecting circulating neutrophils or other immune cells. The overall objective was to identify new, druggable, therapeutic targets for inflammatory joint disease that preferentially affect the pathogenic immune cells responsible for joint damage (e.g. inflammatory neutrophils), with minimal impairment of overall immune function.

We identified a critical role for BCL-XL in the maintenance of neutrophil survival within inflamed tissues, such as those within the joints of RA patients. We found that neutrophils undergo a 'switch' in survival dependency to BCL-XL following exposure to inflammatory cytokines such as GM-CSF and G-CSF, which are produced locally within inflamed joints. This crucial event in the pathogenesis of joint disease extends the survival and thus prolongs the functional effects of inflammatory neutrophils, facilitating ongoing joint damage. Consistent with this, we found genetic ablation or pharmacological antagonism of BCL-XL function using a selective BCL-XL inhibitor (A-1331852), prevented the accumulation of activated neutrophils within the joints of arthritic mice and attenuated disease. Importantly, this had minimal effects on the numbers of circulating neutrophils or most other immune cell populations. Furthermore, we demonstrate that A-1331852 has therapeutic potential by causing apoptosis in human inflammatory neutrophils aspirated from the inflamed joints of patients. Thus, our research has discovered a differential survival requirement in activated neutrophils for BCL-XL and has revealed a new therapeutic approach to neutrophil-mediated joint disease.

Our research was delayed by the COVID-19 pandemic, particularly in the generation and usage of the other conditional BCL-2 family deleter mice. We were able to partially overcome this problem by directly employing specific and well characterized drug inhibitors of the BCL2-survival proteins in our experiments. We will successfully ascertain the role of these survival proteins in arthritis development in vivo using both genetic and pharmacological approaches.

The results of this research have recently been published in Blood Advances.

BCL-XL antagonism selectively reduces neutrophil life span within inflamed tissues without causing neutropenia

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