C-reactive protein (CRP) is an acute-phase protein produced in high quantities by the liver in response to infection and during chronic inflammatory disorders such as rheumatoid arthritis (RA). As a consequence, CRP is in widespread clinical use as a general marker of inflammation. Although CRP is known to facilitate clearance of cell debris by phagocytic cells by binding to its ligand phosphocholine on dead cells, it is still unclear whether CRP displays additional immunological functions.

**Objectives** Here, we set out to investigate whether CRP, which is present in high concentrations in synovial fluid of active RA patients, also plays a role in the orchestration of inflammation in the inflamed joint.

**Methods** Human macrophages were differentiated from blood monocytes of healthy volunteers, or sorted from synovial fluid of RA patients. Cells were stimulated with complexed CRP (c-CRP) and/or ligands for Toll-like receptors (TLRs) and NOD-like receptors (NLRs), mimicking the stimuli in the inflamed joint. Responsible signalling pathways were identified using specific inhibitors and the Sea-son to hTNFtg synovial fibroblasts. Notably, no increased bone marrow derived macrophages, fibroblasts from sost-/-/hTNFtg. Co-culture of synovial fibroblasts and wildtype bone marrow macrophages were analysed by TRAP staining. RANKL expression was measured by ELISA and cytokine expression by array analysis and Western Blot. Moreover, the influence of sclerostin on osteoclastogenesis was additionally analysed in mono-cultures.

**Results** Strikingly, we here provide evidence that CRP is not only a marker, but also a cause of inflammation by strongly amplifying the production of RA-associated pro-inflammatory cytokines. We show that complex formation of CRP as a result of binding to its ligand phosphocholine selectively enhanced TNFα, IL-1β, and IL-23 production by human macrophages. While c-CRP did not induce cytokine production individually, c-CRP synergized with TLRs and NLRs to amplify cytokine gene translation. We identified Fc gamma receptor I and IIa (FcγRI and FcγRIIa) as the main receptors responsible. Moreover, we unravelled the responsible molecular mechanism of c-CRP-induced inflammation, which crucially depends on signalling through kinases Syk and PI3K, resulting in enhanced gene translation of pro-inflammatory cytokines through metabolic reprogramming, particularly through amplified glycosylation and fatty acid synthesis.

**Conclusions** These data indicate that CRP is not only a marker, but also a cause of inflammation in RA patients by selectively promoting RA-associated pro-inflammatory cytokine production by human macrophages, thereby exacerbating pathology. From a therapeutic point of view, inhibition of c-CRP-induced immune activation, e.g. by targeting the identified molecular mechanisms, may be a valuable tool to suppress inflammation.

**Disclosure of interest** None declared.