Correspondence

To the editor:

Reconstitution of protection against *Aspergillus* infection in chronic granulomatous disease (CGD)

We would like to comment on the recent paper by Bianchi and coworkers.1 Patients diagnosed with chronic granulomatous disease (CGD) suffer from recurrent and life-threatening infections. Analysis of clinical data from 429 European CGD patients recently confirmed that *Aspergillus* is a major threat, causing mostly pneumonia but also brain abscesses.2

Reconstitution of an intact X-linked gene encoding gp91phox is a remarkable accomplishment and a promising new therapy for X-CGD. In their *Blood* paper, Bianchi et al correlate the reconstituted nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity in this patient with protection against *Aspergillus* infection, as a result of reconstituted neutrophil extracellular trap (NET) formation. NETs are composed of chromatin decorated with granular proteins and bind Gram-positive and -negative bacteria, as well as fungi, in a nonspecific way. Recently, ex vivo NET formation was shown to depend on superoxide production by activated NADPH oxidase.3 The only empirical data provided by Bianchi and coauthors to underscore the crucial role of NET formation against *Aspergillus* infection are ex vivo observations showing a microbicidal effect of NETs against *Aspergillus* species.

Treating the ex vivo findings as proof of a causal link between (reconstituted) NET formation and protection against *Aspergillus* may be a step too far and may not be essential. NETs do not have any specificity in microbialic activity, whereas CGD patients show a selective susceptibility only to certain microbes.

Moreover, *Aspergillus* infection has recently been studied in a CGD mouse model, and activity of indoleamine 2,3-dioxygenase (IDO) was shown to be crucial for the survival of CGD mouse model, and activity of indoleamine 2,3-dioxygenase in infection.4 IDO converts L-tryptophan into L-kynurenine but the abovementioned relevant findings were not discussed or referred to in the Bianchi paper. It might be possible that reconstitution of other superoxide-dependent steps, such as direct effects or indirectly via IDO activity, rather than the restoration of the capability of NET formation, will protect CGD patients from *Aspergillus* infection.

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References


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