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Defining the molecular basis of immune heterogeneity between individuals using immunoproteomics
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Infection of humans with viral, bacterial or parasitic pathogens, including SARS-CoV2 or Plasmodium spp parasites that cause malaria, can lead to a range of disease manifestations, from asymptomatic responses to mild disease to severe disease to death. This reflects the inherent ability of an individual to control infection, with substantial inter-individual immune heterogeneity now well documented. These heterogenous responses to infection have not yet been explained at a molecular level. Natural or experimental infection with the Plasmodium spp. parasite results in substantial variation in the rate and density of parasite growth. Natural Killer (NK) cells have been associated with Plasmodium parasite control, with distinct differences observed between specific NK cell subpopulations. Taking advantage of a controlled human infection model of P. falciparum, we are applying comprehensive immunological and immunoproteomic approaches to investigate NK cell populations that associate with an individual’s ability to control Plasmodium infection. Bulk proteomics by mass spectrometry, single-cell proteomics by mass cytometry, and single-cell transcriptomics are being applied to specific cell populations of NK cells and other immune cells, to identify proteins and genes associated with parasite control, and immune signatures of responsiveness. Our data suggest that the high-dimensional immune profiling enabled by bulk and single cell proteomics tool will provide important insights into how the pre-infection repertoire of NK cells can influence the outcome of Plasmodium parasite infection in humans. These results would have broad implications beyond malaria, to inform the molecular basis of inter-individual immune heterogeneity.

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ETV6-NTRK3 oncofusion variant interactomes
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Oncogenic fusions, chimeric proteins from two conjoined parental genes, are often not just singular entities but can have breakpoint variation depending where the fusion took place. ETV6-NTRK3 (EN), a fusion between a transcription factor and kinase, is one example of this. Research of EN fusions is mostly restricted to the breakpoint variant that is most commonly found in cancer and could be considered the canonical EN variant. EN fusions, though, have four breakpoint variants which code for a fusion protein with a functional NTRK3 kinase domain and their overall structures are highly similar. Another source of variance is the NTRK3 kinase domain insert, which can be spliced out. Despite structural similarity, there is considerable difference in the rates that the different variants are found in cancer and their tissue distribution. We sought to seek answers to how these four variant differ from each other and does the canonical variant distinguish itself from the other variants. Kinases mainly act through phosphorylation and this requires close interaction, often through adaptor proteins. Therefore, our study is based on interactome analysis. The stable interactions of the canonical EN variant have been studied before and few interactors have been confirmed. Further mystifying the canonical EN variant is the way its breakpoint omits the NTRK3 Y516, an important interaction site of endogenous NTRK3 to downstream pathways. We used BioID and mass spectrometry to find interactors in the near vicinity of the EN variants and also interactors that might relocate after interacting with the EN variants.

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