Inference of the protein interaction network between Fusobacterium nucleatum putative secretome and the human host

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Résumé

F. nucleatum is a gram-negative anaerobic species implicated as key pathogen in gingivitis and periodontitis. It has also been associated to several other inflammatory processes like Inflammatory Bowel Disease [1]. Recently, it has been shown that *F. nucleatum* is prevalent in colorectal cancer patients [2] and may exert its tumorigenic capacity by inducing a pro-inflammatory response [3], an established cancer hallmark. Nevertheless, the causal role of *F. nucleatum* in colorectal cancer and the mechanistic details of host cell functions subversion are not fully understood. To date, only a handful of experimentally verified pathogenic effectors are known and the availability of interaction data with the host is very limited.
In order to tackle these problems, we performed a comprehensive computational analysis to identify putative *F. nucleatum* virulence factors and to infer their interactions with human proteins. By using state-of-the art tools, we predicted 237 *F. nucleatum* proteins as secreted (12% of the proteome). We observed an overrepresentation of functional domains commonly present in known bacterial virulence factors among those proteins. We next sought to identify putative molecular mimicry occurrences (e.g., a bacterial protein element that resembles one of the host at the molecular level and confers a benefit because of this resemblance [4]) in the *F. nucleatum* putative secretome. In particular, we focused on mimicry elements that might mediate the interaction with human proteins. To do so, we analyzed the protein domain composition and their short linear motifs (SLiMs) content [5] and found that 143 *F. nucleatum* secreted proteins have at least one potential mimicry instance. Based on this, we inferred 3746 interactions with 934 human proteins. *Fusobacterium* predicted interactors are (i) mainly localized in the extracellular region and cell membrane, and are involved in immune system activation, inflammatory response, cell adhesion, cancer-related signaling pathways; and (ii) reside in central positions of the human binary interactome and are enriched in known binders of both bacterial and viral proteins [6-7].

By analyzing the structure of the human interactome, we found 31 network modules that are preferentially targeted by *F. nucleatum* secreted proteins and represent cellular functions

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and compartments relevant for the microbe-host cross-talk. We applied a network-based approach we recently developed [8], which integrates patient-based quantitative proteomics data and interaction network analysis, and we found that 3 of these modules are significantly dysregulated during colorectal cancer progression. Overall, our network-based analysis suggests new clues on the molecular basis of *Fusobacterium* – human interaction and may guide future experimental effort to elucidate the contribution of this bacterium in the onset and progression of gut diseases.

References

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