A multiscale signalling network map of immune response in cancer reveals signatures of cell heterogeneity and functional polarization

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To describe the balance between components of tumor microenvironment (TME) and to analyse impact of both non-immune and immune cells, we systematically collected information on related molecular mechanisms and represented in a form of comprehensive network maps. The modular map of cancer associated fibroblasts (CAF), the non-immune component of TME, is composed of 681 objects and 585 reactions. The map is covering the main functions of CAFs in tumor among others, interactions with extracellular matrix components, signalling coordinating involvement of CAFs in tumor growth and interactions of CAFs with immune system. There are two types of functional modules on the CAF maps, modules responsible for CAFs activation are associated with protumor activity and modules involved in CAFs inhibition, therefore contributing to anti-tumor activity. In addition, we constructed signalling maps of macrophages, dendritic cells, myeloid-derived suppressor cells, natural killers, neutrophils and mast cells. These cell type-specific maps integrated together and updated by interactions and crosstalks between them and the map of tumor cell, gave rise to a seamless comprehensive meta-map of innate immune response in cancer. The meta-map contains 1466 objects and 1084 reactions and depicts signaling responsible for anti- and pro-tumor activities of innate immunity system as a whole. The meta-map is represented in a geographical-like manner, possessing a hierarchical structure with two functional zones, each divided into meta-modules and smaller sub-modules. The network maps were applied for identification of possible molecular mechanisms regulating CAF and innate immune cells reprogramming in TME in metastatic melanoma. Unsupervised statistical methods were applied for decomposition of single cell RNASeq data of CAF, natural killers and macrophages. Analysis and interpretation of expression patterns in the context of the network maps demonstrated existence of numerous sub-populations within each cell type characterized by different anti- and pro-tumor functional properties. These network-based polarization signatures correlated with the survival status of patients. We concluded that tumor microenvironment may contain a range of CAF and innate immune cells, varying in their polarization status. The fine-tuned balance between the sub-populations will dictate the overall impact of TME onto tumor evolution in each given case.