Atlas of Cancer Signaling Network: from intracellular networks to tumoral microenviroment

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Studying reciprocal regulations between cancer-related pathways is essential for understanding cancer evolution and response to treatment. With this aim we have constructed the Atlas of Cancer Signaling Network (ACSN, http://acsn.curie.fr), a resource of cancer signaling maps with interactive web-based environment for navigation, curation, data visualisation and computaional analysis (http://navicell.curie.fr). The content of ACSN is represented as a seamless 'geographic-like' map browsable using the Google Maps engine and semantic zooming. The associated blog provides a forum for commenting and curating the ACSN maps content. The atlas contains multiple crosstalks and regulatory circuits between molecular processes implicated in cancer.

ACSN has been initiated as a project focused on intracellular molecular interactions and signaling pathways involved in carcinogenesis. However, many important aspects of tumor behavior such as metastasis, immune response escape, stimulation of angiogenesis cannot be understood without considering the intercellular interactions of cancer cells with their microenviroment. The current step of ACSN development is a systematic and formalized representation of information about molecular mechanisms involved in tumor-microenvironment interactions.

Based on experimental results retrieved from literature by manual curation, we have constructed an integrated signaling networks of innate-immune response and tumor microenvironment. The map compiles information about three major cell types involved in the process, macrophages, dendritic cells and natural killers. We have represented both anti- and pro-tumor aspects of immune response signaling of these cell types. It represents signaling at two scales first, intracellular signaling involved in the regulation of each

individual type of immune cells while interacting with tumor cell and with tumor microenvironment; second, intercellular signaling describing crosstalk between different immune cell types and tumor cell.

The maps were used for visualization and analysis of expression data from different molecular subtypes of breast-cancer tumors and demonstrated a significant correlation between activation of immunosuppressive signaling modules and tumor aggressiveness. The new resource is a powerful and flexible tool for modeling pathways involved in tumorigenesis and immune response and expression data analysis. We are planning to apply the same approach to the reconstruction of other aspects of tumor-microenvironment interactions such as adaptive immune response, interaction with tumor associated fibroblasts, angiogenesis, and create a complete molecular network of tumor microenvironment and immune response involved in cancerogenesis. The new maps will be integrated into ACSN and will enrich the cancer-related signaling representation, providing an opportunity to develop personalized cancer treatment strategies and improve patient stratification considering the various types of immune–related signaling pathways.

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