TRANSCRIPTION AND CHROMATINE

PROJECT 1

Project title
"Characterization of transcriptional and epigenetic regulators of macrophage activation"

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Laboratory name: Transcription and Chromatin

Abstract
Tissue responses to microbial and endogenous danger signals involve the activation of both resident and monocyte-derived macrophages, as well as the coordinated inducible expression of hundreds of inflammatory genes. Gene transcription is controlled by the information contained in thousands of genomic regulatory elements (enhancers and promoters), which is first read by transcription factors (TFs) and then integrated and relayed to the transcriptional machinery via an array of co-regulators with disparate biochemical activities and functions. The recent work of several groups, including our own, has extensively characterized how in macrophages the genomic regulatory sequences controlling inflammatory gene expression are coordinately bound and activated by myeloid lineage-determining TFs and broadly expressed stimulus-activated TFs. However, we still have a very incomplete understanding of the necessary next step in the process, namely how distinct combinations of DNA-bound TFs regulate recruitment and function of the co-regulators and machineries that control gene transcription.

Main technical approaches
Transcriptomics and epigenomic analyses on mouse macrophages.

Scientific references
Cooptation of tandem DNA repeats for the maintenance of mesenchymal identity (C. Balestrieri, G. Alfarano, M. Milan, V. Tosi, E. Prosperini, P. Nicoli, A. Palamidessi, G. Scita, G.R. Diaferia, G. Natoli). Cell 173:1150-1164 (2018)
Opposing macrophage polarization programs show extensive epigenomic and transcriptional cross-talk (Piccolo V., Curina A, Genua M, Ghisletti S, Simonatto M, Sabo' M, Amati B, Ostuni R, Natoli G). Nature Immunology 18, 530-540. PMID 28288101 (2017).

High constitutive activity of a broad panel of housekeeping and tissue-specific cis-regulatory elements depends on a subset of ETS proteins (Curina A, Termanini A, Barozzi I, Prosperini E, Simonatto M, Polletti S, Silvola A, Soldi M, Austenaa L, Bonaldi T, Ghisletti S, Natoli G) Genes & Development 31,399-412. PMID 28275002. (2017).

Transcriptional determination and functional specificity of myeloid cells: making sense of diversity (Monticelli S., Natoli G.) Nature Reviews Immunology 17, 595-607 (2017)

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PROJECT 2

Project title

"An integrative genomic approach to understand the transcriptional bases of intratumoral heterogeneity in human PDACs"

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Abstract

The causes of this extremely aggressive clinical behaviour of pancreatic cancer are both the advanced stage of the disease at diagnosis and the biological properties of this tumor type. A remarkable feature of human PDACs is the co-occurrence within the same tumor of completely different and morphologically identifiable components: well-differentiated (low-grade) epithelial structures and nests of poorly differentiated (high-grade) quasi-mesenchimal tumor cells, whose coexistence reflects distinct underlying gene regulatory networks and transcriptional outputs. Because clonal cell lines generated from human PDACs stably retain the ability to selectively generate either homogeneously well-differentiated or homogeneously poorly-differentiated tumors when xenografted into nude mice, it can be hypothesized that the transcriptional programs enforcing differentiation are hardwired in the different genetic makeup of the highly heterogeneous tumor cells present in each individual PDAC. Moreover, large scale genomic analyses indicate that PDAC intra-tumor heterogeneity may be generated at very early stages of tumorigenesis by a rapid series of catastrophic mitotic errors.

This project is motivated by the assumption that the heterogeneity of human PDACs is a critical determinant of the peculiar clinical properties (and specifically the resistance to therapy) of these tumors. Our aim is to obtain a molecular characterization and mechanistic understanding of the transcriptional bases of cellular variability, eventually leading to the identification of novel mechanism-aware therapeutic options.

Main technical approaches

Transcriptomics and genomics on human PDAc samples.

Scientific references

Cooptation of tandem DNA repeats for the maintenance of mesenchymal identity (C. Balestrieri, G. Alfarano, M. Milan, V. Tosi, E. Prosperini, P. Nicoli, A. Palamidessi, G. Scita, G.R. Diaferia, G. Natoli). Cell 173:1150-1164 (2018)

Dissection of transcriptional and cis-regulatory control of differentiation in human pancreatic cancer (G. Diaferia, C. Balestrieri, E. Prosperini, P. Nicoli, P. Spaggiari, A. Zerbi, G. Natoli). EMBO Journal 35, 596-617 PMID: 26769127 (2016).