Genomic and functional analysis of gynecological carcinosarcomas

Anne-Sophie Sertier¹, Isabelle Treilleux, Sandrine Boyault, Anthony Ferrari, Mojgan Devouassoux-Shisheboran, Janice Kielbassa, Laurie Tonon, Vincent Le Texier, Emilie Thomas, Anne-Pierre Morel, Roxane Pommier, Amandine Charreton, Anne Floquet, Florence Joly-Lobbedez, Dominique Berton-Rigaud, Gwenaél Ferron, Laurent Arnould, Sabrina Croce, Guillaume Bataillon, Pierre Saintigny, Eliane Mery-Lamarche, Christine Sagan, Ivo Gut, Fabien Calvo, Alain Viari, Isabelle Ray-Coquard, **Alain Puisieux**²

Introduction

Gynecological carcinosarcomas (GCS) are histologically defined as biphasic neoplasms composed of an intimate admixture of carcinomatous epithelial and sarcomatous malignant components. Although these tumors represent a small fraction of newly diagnosed uterine or ovarian cancers, they disproportionately contribute to the population of patients recurring and dying from disease. Due to their rarity and to their histological complexity, genetic and functional studies on GCS are scarce and the intimate mechanisms of initiation and development of these highly aggressive and heterogeneous neoplasms remain largely unknown.

Carcinosarcoma dataset

A collection of 18 GCS, including 13 endometrial GCS (**UCS**) and 5 ovarian GCS (**OCS**), was established. Two distinct regions of each tumor were dissected and whole genome sequencing, RNA sequencing and methylation array profiling were performed to determine the genomic and DNA methylome landscapes of GCS.

Molecular characteristics

Structural variants

Single nucleotide variants

Mutational signatures

Results

The evaluation of evolutionary histories of GCS in 5 tumors with pure carcinomatous and sarcomatous elements demonstrated that these elements shared many somatic alterations (mutations, structural variants and copy number variations), establishing unambiguously the common genetic origin of these malignancies.

Pathway alterations

slightly modified from Sanchez-vega *et al.*, Cell 2018

Epigenetic modifiers and chromatin remodeling factors

from Roy *et al.*, Cell 2014

EMT process in Carcinosarcomas

Differential methylome analysis

miR200c and miR141 are methylated in sarcoma components and are demethylated in carcinoma components

Co-occurring alterations :

triade [TP53 + PI3K pathway + Epigenetic regulators]

Uterine carcinomas with the triade [TP53+PI3K pathway+ epigenetic regulators] (26%) show an EMT signature.

Conclusion

The most prominent mutations in GCS were TP53 mutations, mutations affecting the PI3K pathway genes and mutations affecting chromatin remodeling genes. The finding that root mutations in GCS are also frequent in gynecological carcinomas (compared from TCGA) strongly supports an epithelial origin of GCS with a progressive evolution relying upon a transdifferentiation process. This dynamic notion implies that carcinosarcomas are the end result of an evolutionary process and that early forms of GCS may be histologically classified as carcinomas.