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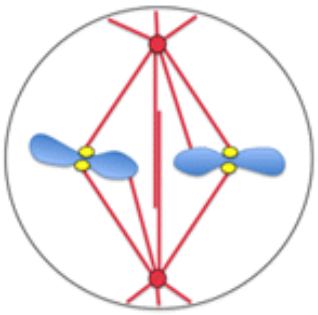
ITMO Cancer



Ariane Abrieu / Nathalie Morin

Mechanisms of Mitosis

/ / Debant Anne CNRS / University

Long-term expertise in the mitosis field are used to decipher mechanisms at play during sarcoma metastasis

Research brief

Soft tissue sarcomas are poorly characterized tumors due to their extreme heterogeneity, and do not benefit from targeted chemotherapies. A genome-wide transcriptomic survey recently defined a 67 genes signature (CINSARC) whose overexpression (CINSARC+) predicts metastatic outcome. The CINSARC signature is composed of genes involved in mitosis, including more than half of the mitotic kinases and kinesins, which are the focus of the research in our team. Cell lines are derived form sarcoma operated at the Bergonie Institute, and their genome-wide transcriptomic profiles are determined (Dr Chibon, Bordeaux, ongoing collaboration). Our preliminary results show that the CINSARC+ cell lines do not have accelerated cell cycle kinetics, and do not spend more time in mitosis than the CINSARC- cell lines. This rules out the hypothesis that mitotic genes are overexpressed in these cell lines (and primary tumors) due to their hyperproliferative status. We plan to isolate the sarcoma initiating cells from these cell lines in order to analyze the earliest appearance to resistance to chemotherapies. In addition, we are currently studying the hypothesis that deregulation of mitotic proteins expression favors the invasive potential of these tumors. Eventually, we will test whether these findings may open new therapeutic windows.

Methodologies used

- - Cell culture of lines derived from primary tumors for which the transcriptomic profiles (from original tumor & derived cell line) are available
- - Time lapse microscopy, immunofluorescence and western blot to determine spatio-temporal deregulation of mitotic proteins and associated phenotypes
- - High-content screening to test the viability (IG50) of various cell lines using small molecules targeting mitotic kinases and kinesins, actin and microtubule cytoskeleton, small GTPases, alone or in combinations (putative synergies)
- - 3D invasion assays in collagen. Determination of sensitivity to various drugs
- - Flow cytometry to isolate the side-population of cells that efflux the drugs more efficiently, i.e. the cells most difficult to eradicate.

Publications

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Patents, pending/registered

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Key Facts

- ***Team :***

  Researchers : 4
  Technicians : 2
  PhD students : 0
  Postdoc fellows : 1

- ***Translational approaches :***

  Patents : 0
  Clinical research grants : 3
  Industry partners : 0

- ***International research links :***

Keywords

- Sarcoma
- Metastasis
- Mitosis
- Kinase
- Cytoskeleton
- Cell culture
- High-content screening
- High-resolution imaging
- 3D invasion assays
- Xenograft

Biological resources

- Obtained via collaboration