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Press Release

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Cancer: Tumor driver promoting EMT, metastasis and resistance to therapy

Publication in ***Nature***: researchers at the Université Libre de Bruxelles (ULB) identify, for the first time, the functions of *FAT1,* one of the most frequently mutated cancer gene drivers. They uncover that *FAT1* mutations promotes invasive features, metastasis and resistance to commonly used anti-cancer drugs, and discover new therapy for FAT1 mutated cancers.

Cancer metastasis, which is the dissemination of tumor cells into distant organs, is the leading cause of mortality in cancer patients. To undergo metastasis, cells must leave the primary tumor, circulate into the blood, colonize distant organs, and form distant metastasis. It has been proposed that epithelial to mesenchymal transition (EMT), a process in which epithelial cells detach from their neighboring cells, and acquire mesenchymal migrating properties, is important to initiate the metastatic cascade allowing the cancer cells to leave the primary tumor. However, the role of genetic mutations in promoting EMT is unknown.

FAT1 is among the most frequently mutated driver genes in a broad range of human cancers. The loss of function mutations in this gene suggest that *FAT1* acts as tumour suppressor, preventing cancer development. However, and despite the high frequency of *FAT1* mutations, its role in cancer is poorly understood.

In a study published in ***Nature***, researchers led by **Prof. Cedric Blanpain**, MD/PhD, WELBIO investigator, Director of the Laboratory of Stem Cells and Cancer and Professor at the Université Libre de Bruxelles, Belgium, demonstrated, for the first time, that loss of *FAT1*, promote EMT, invasive features and metastasis in skin squamous cell carcinoma -the second most frequent cancer in humans-, lung cancer -the deadliest cancer - and head and neck tumors.

Ievgenia Pastushenko and colleagues used state of the art genetic models of skin and lung cancers, as well as human skin, lung and head and neck tumors to assess the role of *FAT1* in cancer. The authors discovered that loss of function of *FAT1*, promotes hybrid EMT phenotype, characterized by the co-expression of epithelial and mesenchymal genes in tumor cells. The authors demonstrated that this hybrid EMT state occurring following *FAT1* loss of function, promotes metastasis and was associated with poor clinical outcome in patients with lung cancers. "It was particularly exciting to identify that mutations in a single gene, *FAT1*, promote hybrid EMT state, leading to metastasis and associated with poor prognosis in cancer patients" comments **Ievgenia Pastushenko**, the first author of this study.

Using different molecular approaches, the authors decipher the mechanisms by which *FAT1* mutations promote hybrid EMT state. "The identification of the mechanisms that promote this highly metastatic tumor state, allowed us to identify drug resistance and vulnerabilities in FAT1 mutated cancers. We found that Fat1 mutated cancers are highly resistant to several drugs including EGFR inhibitor that are frequently used to treat patients with lung cancers. Most interestingly, we identify that *FAT1* mutated cancers are particularly sensitive to other drugs including Src inhibitor that are currently used to treat patients with blood cancer. These findings will have very important and immediate implications for personalized therapy in patients *FAT1* mutated cancers", comments **Pr Cedric Blanpain**, the senior author of this study.

This study is a result of a fruitful collaboration between different research groups and clinical departments in Belgium, France and Spain. In Belgium, the teams of Pr Isabelle Salmon and other departments from the Hospital Erasme, Brugman Hospital, as well as Institute Bordet, Cliniques d'Europe, KU Leuven and VIB participated in the study. In France, Francoise Helmbacher from Universités de Marseille et Manuel Thery from Université de Paris participated in this study. In Spain, Spanish Academy of Dermatology and the Hospitals Ramon y Cajal (Madrid), Hospital Clinic (Barcelona), Hospital Clinico Lozano Blesa (Zaragoza), Complejo Asistencial de Leon (Leon), Clinica Universitaria de Navarra (Pamplona), Hospital Costa del Sol (Marbella) and Instituto Valenciano de Oncologia (Valencia) participated in the study.

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