SCIENCE AT THE EDGE

2016 SEMINAR SERIES

Quantitative Biology Graduate Program | Gene Expression in Development and Disease

Sarah-Maria Fendt

VESALIUS RESEARCH CENTER

"A perfect match: How the nutrient microenvironment supports metastasis formation and progression"

Cancer progression towards metastasis formation is the leading cause of death incidences in cancer patients. During metastasis formation and progression cancer cells need to adapt their overarching cellular phenotype and are challenged with alterations in the nutrient microenvironment. Both of these processes require changes in cancer cell metabolism that can be targeted for therapy. We are studying the metabolism of cancer cells during metastasis formation and progression using *in vitro* and *in vivo* ^{13}C tracer analysis in 2D and 3D culture systems as well as metastatic breast cancer mouse models. We discovered that during metastasis formation, the survival and colonization capacity of breast cancer cells is dependent on the activity of proline dehydrogenase, which fuels mitochondrial energy production. We further found that inhibition of proline dehydrogenase is sufficient to inhibit growth in 3D cultures and reduce metastasis formation *in vivo*. Moreover, we discovered that once metastases are established the nutrient availability within organ microenvironment defines the mode of anaplerosis breast cancer cells use to refill the TCA cycle for biomass production. Specifically, we found that the nutrients available within the lung microenvironment induce pyruvate carboxylase dependent anaplerosis via enzyme kinetics and decrease the need of breast cancer cells for glutamine anaplerosis. Taken together we show that phenotypic switches during metastasis formation require energy production from proline catabolism, while cancer cells are flexible to adapt their biomass production to the nutrients available within the organ microenvironment.

Key publications: ([#]equal corresponding authors *authors listed in alphabetic order)

Christen S, Lorendeau L, Schmieder R, Broekaert D, Metzger K, Veys K, Buescher JM, Orth MF, Davidson SM, Grünewald TGP, De Bock K & **Fendt S-M**: *Breast cancer-derived lung metastases show increased pyruvate carboxylase-dependent anaplerosis*. **Cell Reports**, accepted; **2016**

Schoors S, Bruning U, Missiaen R, Queiroz KCS, Borgers G, Elia I, Zecchin A, Cantelmo AR, Christen S, Goveia J, Heggermont W, Goddé L, Vinckier S, Van Veldhoven PP, Eelen G, Schoonjans L, Gerhardt H, Dewerchin M, Baes M, De Bock K, Ghesquière B, Lunt SY, **Fendt S-M**[#] & Carmeliet P[#]: *Fatty acid synthesis is essential for dNTP synthesis in endothelial cells*. **Nature**; 520(7546):192-7; **2015**

Buescher JM, Antoniewicz MR[*], Boros LG[*], Burgess SC[*], Brunengraber H[*], Clish CB[*], DeBerardinis RJ[*], Feron O[*], Frezza C[*], Ghesquiere B[*], Gottlieb E[*], Hiller K[*], Jones RG[*], Kamphorst JJ[*], Kibbey RG[*], Kimmelman AC[*], Locasale JW[*], Lunt SY[*], Maddocks ODK[*], Malloy C[*], Metallo CM[*], Meuillet EJ[*], Munger J[*], Nöh K[*], Rabinowitz JD[*], Ralser M[*], Sauer U[*], Stephanopoulos G[*], St-Pierre J[*], Tennant DA[*], Wittmann C[*], Vander Heiden MG[*], Vazquez A[*], Vousden K[*], Young JD[*], Zamboni N[*] & **Fendt S-M**: *A roadmap for interpreting ^{13}C metabolite labeling patterns from cells.* **Current Opinion in Biotechnology**; 34:189-201; **2015**

FRIDAY, NOVEMBER 4, 2016

11:30 AM, ROOM 1400 BPS

Refreshments at 11:15

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