Mechanisms and therapeutic targeting of the neuronal NMDAR signaling pathway promoting breast cancer pathogenesis

Project

Simge Yücel

Simge Yücel is joining the Hanahan research group to pursue her PhD. She will conduct her thesis research in the Hanahan lab in the AGORA Translational Cancer Research Building, co-supervised by Prof. Douglas Hanahan and Prof. Michele De Palma, who will also be based in the AGORA.

The research will focus on elucidating pathogenic mechanisms and exploring innovative therapeutic targeting strategies for breast cancer. The focus will be on a neuronal signaling pathway – centered upon the NMDA receptor (NMDAR) – that the Hanahan lab discovered to be hijacked by cancer cells to enhance invasion and metastasis, the hallmarks of malignancy that cause cancer mortality. The NMDAR's role in cancer pathogenesis was initially discovered and described in 2013 (Li & Hanahan, Cell), and further characterized in 2018 (Li, Zeng *et al.*, Cancer Cell), principally in pancreas cancer. Then in 2019, the role of NMDAR signaling in the metastasis of breast cancer to the brain was established in a major article in Nature (Zeng *et al.*). Unpublished data from the Hanahan lab suggest that the NMDAR may also be hijacked in certain primary breast tumors and in metastasis to other sites. Simge Yücel will use mouse models of breast cancer in conjunction with analysis of human breast cancer biopsies to pursue the following lines of investigation:

1. What are the effects of conditional, cancer cell-specific genetic ablation of the key signaling subunit of NMDAR (GluN2B) on the development and lethal progression of invasive primary and lung-metastatic tumors in the MMTV-PymT mouse model of breast cancer? (The 2013 *Cell* publication showed that the NMDAR is activated in this model.) Other models, e.g. the C3Tag transgenic model of triple negative breast cancer, may also be employed. The plan is to assess not only invasion and metastasis but also effects on the tumor microenvironment, using a portfolio of sophisticated histopathological, cellular and molecular '-omic' technologies, including single cell RNA sequencing.

2. Similarly, Simge Yücel will assess the effects of conditional cancer-specific deletion of candidate downstream effectors of NMDAR described in the 2018 *Cancer Cell* publication, in particular the transcription factor HSF1 and the translational regulator FMRP. She will use engineered breast cancer cell lines in culture and as transplant tumors to further investigate these effectors and to identify key genes amongst the myriad of genes regulated by each one.

3. She will work with collaborators in Lund, Sweden, and Bern to assess tissue microarrays of human breast cancer for expression of components of the NMDAR signaling pathway, and in particular diagnostic pathway activity, as revealed by immunostaining for phosphorylated GluN2B. She will look for correlations with

histological and molecular subtypes of human breast cancer, and associations with poor survival. She will study both primary breast tumors and metastases to other organs, such as lung, liver, and bone. She will develop hypotheses which she will then test in appropriate mouse models of breast cancer.

4. Simge Yücel will explore mechanism-guided therapeutic targeting strategies aimed to pharmacologically inhibit either NMDAR signaling or genetically validated downstream effectors of its malignancy-enhancing program, in particular to impair invasion and metastasis. She will test rational combinations with drugs that disrupt other key tumor progression pathways, or that modulate the immune system so as to promote the efficacy of immunotherapy.

These lines of investigation are likely to reveal new opportunities, which will be incorporated in the research.

References

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- Li, L., Zeng, Q., Bhutkar, A., Galvan, J., Karamitopoulou, E., Noordermeer, D., Peng, M.W., Piersgilli, A., Perren, A., Zlobec, I., Robinson, H., Iruela-Arispe, M.L., & Hanahan D. (2018) GKAP acts as a genetic modulator of NMDAR signaling to govern invasive tumor growth. Cancer Cell, 33: 736-751.
- Zeng, Q., Michael, I.P., Zhang, P. Saghafini, S., Knott, G., Jiao, W., Brian D. McCabe, B.D., José A. Galván, J.A., Robinson, H.P.C., Zlobec, I., Ciriello, G., and Hanahan, D. (2019). Synaptic proximity enables NMDAR signaling to promote brain metastasis. Nature, 573: 526-531.