LGR5, The Moving Target

LGR5 Is a Dynamic Protein and Changes in LGR5 Expression Can Allow Cancer Cells to Resist Treatment and Metastasize[1–6]

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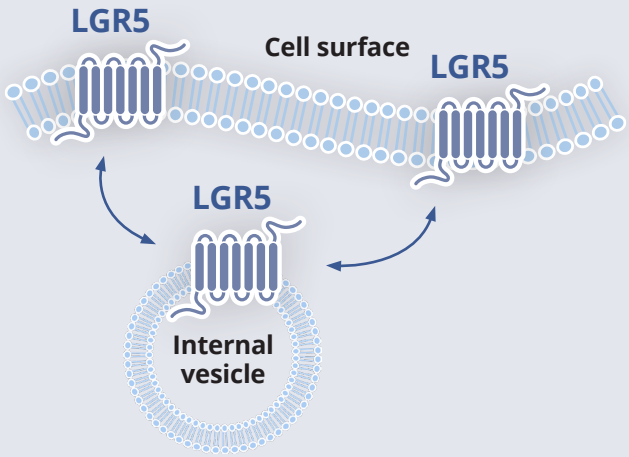
LGR5 Is a Dynamic Protein That Is Constantly on the Move[1,2]

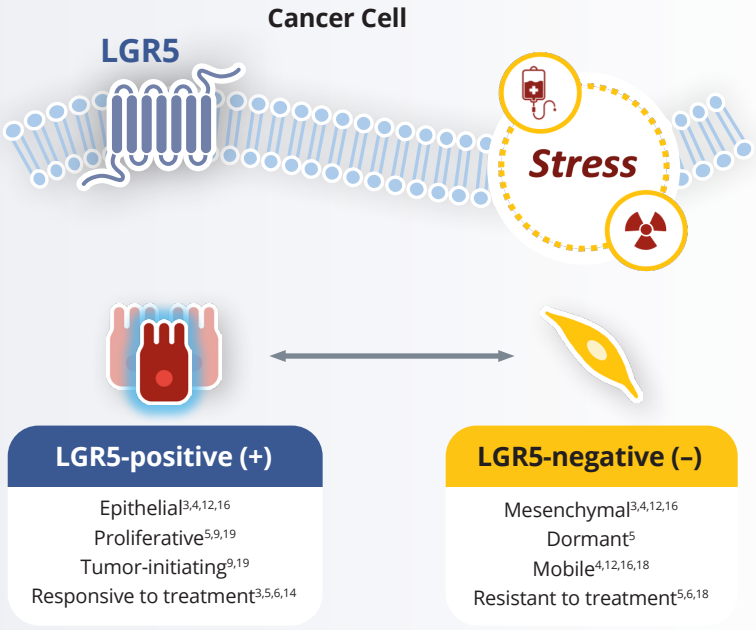
- LGR5 protein is constantly recycled at the cell surface, always being added and removed (regardless of ligand binding)[1,2]
- This dynamic allows cancer cells to adapt to changes in the tumor microenvironment[1,2,7,8]
- LGR5 is currently *not* an actionable biomarker[9,10,a]



[a]LGR5 protein detection is possible for preclinical purposes (eg, western blot, live cell imaging),[11] but a suitable, well-validated antibody for human sample testing is not currently available[9,10]
LGR5, Leucine-rich repeat–containing G protein–coupled receptor 5.

Changes in LGR5 Expression Allow Cancer Cells to Resist Treatment and Metastasize[3–6,12]

- Preclinical models show that:
  - LGR5 expression is silenced when cancer cells are subjected to stress (eg, chemotherapy, radiation)[3,5,6,13]
  - **LGR5 expression increases when cancer cells are treated with EGFR-targeted therapy[11,14,15]**
  - LGR5 expression is silenced when epithelial cancer cells transition to a mesenchymal state, shedding stationary characteristics and becoming mobile[3,4,12,16]
- Changes in LGR5 expression are reversible[3,4,17,18]
  - Transitioning between LGR5-positive and LGR5-negative states allows cancer cells to change phenotype and behavior[3,4,8,12,16–18]



EGFR, epidermal growth factor receptor.

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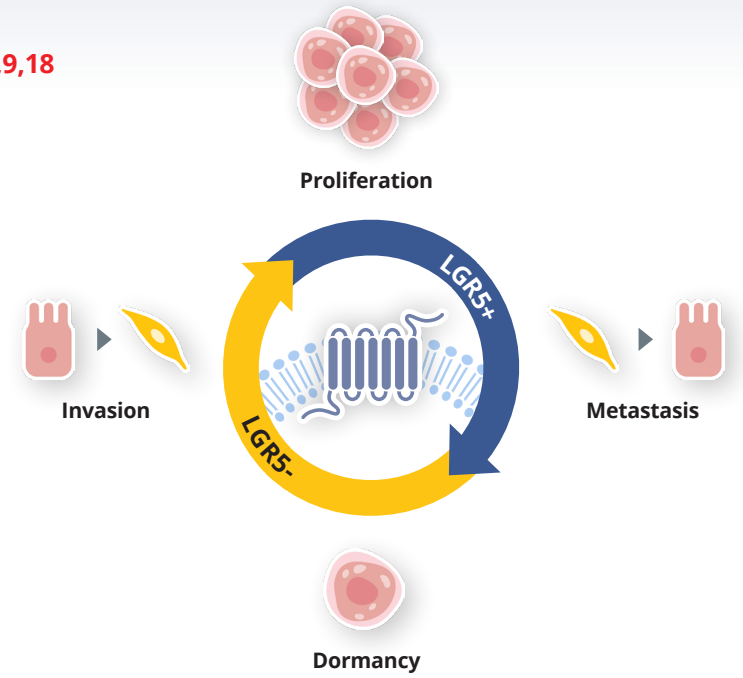
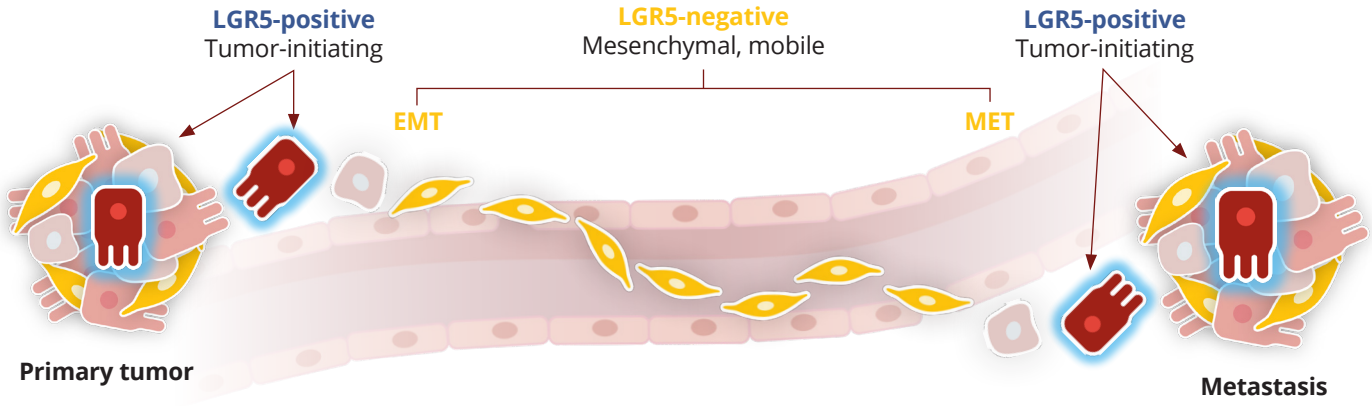
LGR5 Can Regulate Cancer Progression and Resistance[5,7,9,18]

- LGR5 expression is dynamic and cancer cells can turn it on and off[3,4,18]
  - When LGR5 expression is "on," cancer cells are able to proliferate and initiate tumors[5,9,19]
  - When LGR5 expression is "off," cancer cells stop proliferating and can travel away from the primary tumor[4,5,12,16,18]
- This dynamic of LGR5 silencing and reactivation regulates pathogenic plasticity and enables treatment resistance and disease progression[3–6,12,18]
  - **Is there a connection between LGR5 and resistance to EGFR-targeted therapy?[14,a]**
- Because LGR5 is a moving target,[1,2,7,8] developing a therapeutic strategy for it may require the integration of other targets or pathways[15,18,20–22]

[a]EMT is a known resistance mechanism to EGFR-targeted therapy[23–25]





EMT, epithelial-mesenchymal transition; MET, mesenchymal-epithelial transition.

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1. Carmon KS, et al. *Mol Cell Biol.* 2012;32(11):2054-2064; **2.** Snyder JC, et al. *J Biol Chem*. 2013;288(15):10286-10297; **3.** Fey SK, et al. *Cell Rep*. 2024;43(6):114270; **4.** Fumagalli A, et al. *Cell Stem Cell.* 2020;26(4):569-578; **5.** Kobayashi S, et al. *Stem Cells.* 2012;30(12):2631-2644; **6.** Posey TA, et al. *Mol Cancer Ther.* 2023;22(5):667-678; **7.** Morgan RG, et al. *Br J Cancer.* 2015;112(4):714-719; **8.** Okamoto Y, et al. *J Biol Chem.* 2020;295(14):4591-4603; **9.** Conti S, et al. *Nat Commun.* 2024;15(1):3363; **10.** Asfaha S, et al. *Cell Stem Cell.* 2015;16(6):627-638; **11.** Basak O, et al. *Cell Stem Cell.* 2017;20(2):177-190 e174; **12.** Shimokawa M, et al. *Nature.* 2017;545(7653):187-192; **13.** High PC, et al. *Cell Rep Med.* 2025;6(10):102363; **14.** Walker F, et al. *PLoS One.* 2011;6(7):e22733; **15.** Ge Y, Fuchs E. *Nat Rev Genet.* 2018;19(5):311-325; **16.** High PC, et al. *Trends Cancer*. 2026; Apr 6:S2405-8033(26)00037-3; **17.** de Sousa e Melo F, et al. *Nature*. 2017;543(7647):676-680; **18.** Leung C, et al. *Trends Cell Biol.* 2018;28(5):380-391; **19.** Barker N, et al. *Nature.* 2009;457(7229):608-611; **20.** Cao W, et al. *Nat Commun.* 2020;11(1):1961; **21.** Morgan RG, et al. *Br J Cancer*. 2018;118(4):558-565; **22.** Xu L, et al. *Stem Cell Res Ther*. 2019;10(1):219; **23.** Mueller N, et al. *Immunother Adv.* 2025;5(1):ltaf017; **24.** Carosi F, et al. *Crit Rev Oncol Hematol*. 2026;221:105207; **25.** Chhouri H, et al. *Cancers (Basel)*. 2023;15(2):504; **26.** Zhou J, et al. *J Exp Clin Cancer Res*. 2021;40(1):328.

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