LGR5 Key Takeaways

LGR5 Is a Dynamic Stem Cell Protein That Can Be Exploited by Common Carcinomas Including Head and Neck, Colorectal, and Lung[1–7]

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Epithelial Cancers (Carcinomas) Are Common and Have a Poor Prognosis Despite an Established Treatment Target, EGFR[7–9]

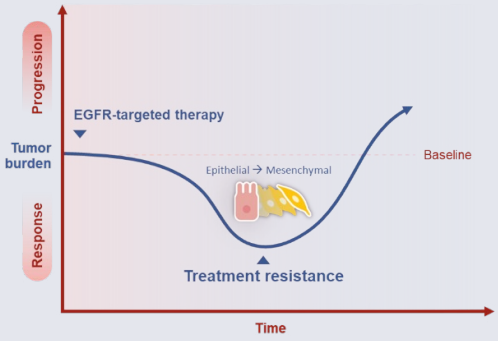


Figure is hypothetical and does not reflect data from a specific clinical study.[18-20]

- Head and neck cancer (H&N), colorectal cancer (CRC), and lung cancer (NSCLC) are examples of epithelial cancers[9,10]
  - Collectively these cancers account for approximately 450,000 new cases and 200,000 deaths annually in the US (2026 estimate)[7]
- **Pathogenic plasticity is an emerging cancer hallmark and treatment resistance to EGFR-targeted therapy (via EMT) is an example[11–14]**
  - EMT is the process of epithelial cells losing their stationary characteristics (eg, cell-to-cell adhesion) and acquiring mesenchymal traits that facilitate motility and invasion[15,16,a]
  - Mesenchymal-epithelial-transition (MET) is the complimentary process where epithelial characteristics are restored[16]

[a]"Mesenchymal" refers to cells that develop into connective tissue, blood vessels, and lymphatic tissue.[17]
EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; NSCLC, non-small cell lung cancer.

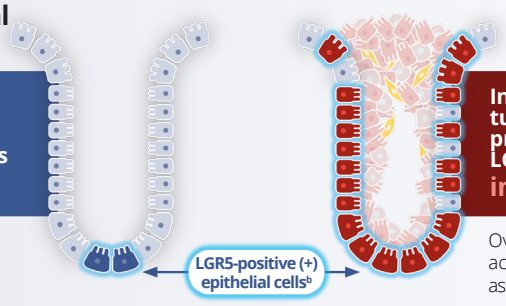
Cancer Cells That Unlock LGR5 Expression Acquire Pathogenic Plasticity and Can Initiate Tumors[3,5,21]

- In a healthy setting, adult stem cells in epithelial tissue express a protein called LGR5[3]
  - LGR5-positive cells support tissue homeostasis and regeneration[3]
  - In the intestine, LGR5-positive cells are a small population of highly proliferative cells (<10% of basal crypt) that replace epithelial cells lost to shedding[5,22,23]
- In a pathogenic setting, cancer cells can unlock LGR5 expression, which enables tumor initiation[3,5,21]
  - In the initial stages of colorectal tumorigenesis, the percentage of LGR5-positive cells can increase dramatically (10-fold; 70% of basal crypt)[5]
  - This allows cancer cells to attain stem-cell–like capabilities (pathogenic plasticity) that enable proliferation and differentiation[3,21,24,25]

Colorectal tumorigenesis

Basal crypt of normal intestine

LGR5-positive cells are a small population of highly proliferative cells (<10%)[5,22,23]



Tumor initiation[a]

In colorectal tumorigenesis, the proportion of LGR5-positive cells can increase 10-fold[5]

Overexpression of LGR5 occurs across carcinomas and has been associated with poor outcomes[3,4,6,26–28]

LGR5, Leucine-rich repeat–containing G protein–coupled receptor 5.
[a]Adenomas and well/moderately differentiated adenocarcinomas.[5,29]
[b]Based on in situ hybridization (ISH) analysis of LGR5 mRNA expression.[5]

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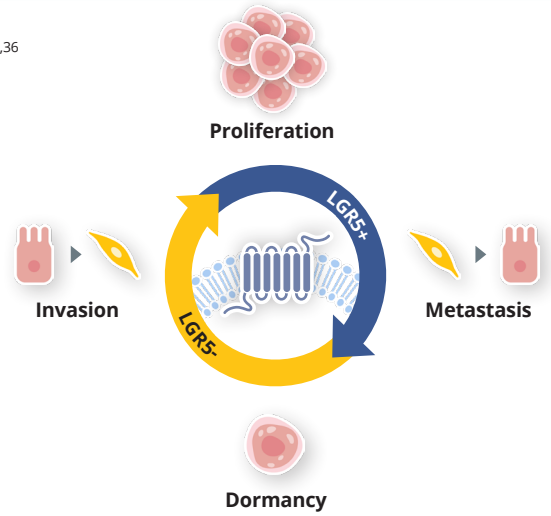
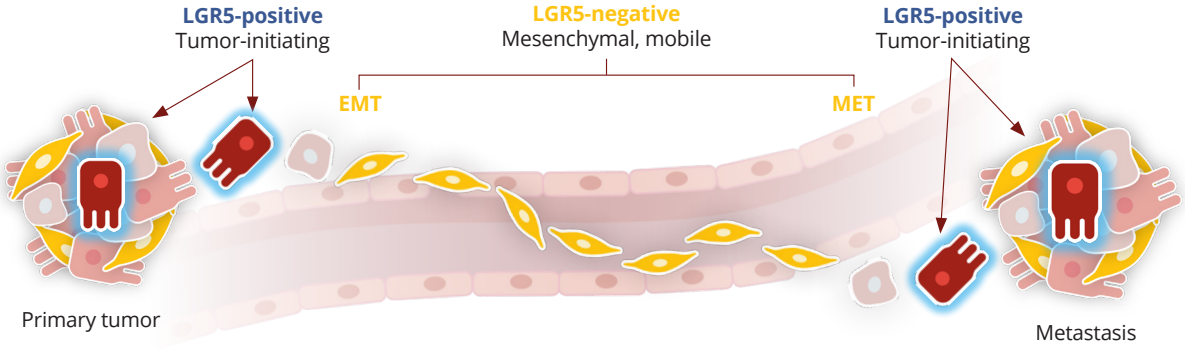
LGR5 Is a Dynamic Regulator of Pathogenic Plasticity[30–35]

- LGR5 is a dynamic protein that is constantly recycled at the cell surface[1,2]
  - Cancer cells can use this dynamic to turn LGR5 expression on/off,[31,33,35,36] and adapt to stress (eg, chemotherapy, radiation)[35,37–39]
- **Is there a connection between LGR5 and resistance to EGFR-targeted therapy?[40]**
  - Cancer cells can transition between LGR5-positive and LGR5-negative states to change their activity, resist treatment, and metastasize[30–36,38,39,41]
  - Preclinical data show that LGR5 expression increases when cancer cells are treated with EGFR-targeted therapy[40,42,43]
  - LGR5 expression is silenced during epithelial-mesenchymal transition (EMT),[30,31,34,41] which is a resistance mechanism to EGFR-targeted therapy[12–14]
- Because LGR5 is a moving target,[1,2,33,36] developing a therapeutic strategy for it may require the integration of other targets or pathways[28,35,42,44,45]
  - LGR5 is currently *not* an actionable biomarker[3,25]
  - LGR5 protein detection is possible for preclinical purposes (eg, western blot, live cell imaging),[43] but a suitable, well-validated antibody for human sample testing is not currently available[3,25]





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

See the full LGR5 story at CancersWildCard.com

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.** Leung C, et al. *Trends Cell Biol.* 2018;28(5):380-391; **4.** Rot S, et al. *BMC Cancer.* 2019;19(1):155; **5.** Martin ML, et al. *Cell Signal.* 2018;42:97-105; **6.** Gao F, et al. *Transl Cancer Res.* 2019;8(1):203-211; **7.** Siegel RL, et al. *CA Cancer J Clin.* 2026;76(1):e70043; **8.** Halder S, et al. *Expert Opin Ther Targets.* 2023;27(4-5):305-324; **9.** Cleveland Clinic. Carcinoma. Accessed March 2026. https://my.clevelandclinic.org/health/diseases/23180-carcinoma; **10.** Tahayneh K, et al. *J Clin Med.* 2025;14(3):1025; **11.** Hanahan D. *Cancer Discov.* 2022;12(1):31-46; **12.** Chhouri H, et al. *Cancers (Basel).* 2023;15(2):504; **13.** Zhou J, et al. *J Exp Clin Cancer Res.* 2021;40(1):328; **14.** Carosi F, et al. *Crit Rev Oncol Hematol.* 2026;221:105207; **15.** Makitie AA, et al. *Head Neck.* 2019;41(10):3712-3718; **16.** Thompson EW, et al. *Nat Rev Clin Oncol.* 2025;22(10):711-733; **17.** National Cancer Institute. Mesenchymal. Accessed March 2026. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/mesenchymal; **18.** Kobayashi K. *J Respir.* 2023;3:223-236; **19.** Ciardiello D, et al. *JAMA Netw Open.* 2024;7(4):e245635; **20** Khattri A, et al. *Cancer Gene Ther.* 2024;31(10):1477-1485; **21.** Barker N, et al. *Nature*. 2009;457(7229):608-611; **22.** Barker N, et al. *Nature.* 2007;449(7165):1003-1007; **23.** de Lau W, et al. *Genes Dev.* 2014;28(4):305-316; **24.** Torborg SR, et al. *Trends Cancer.* 2022;8(9):735-746; **25.** Mueller N, et al. *Immunother Adv.* 2025;5(1):ltaf017; **26.** Stanisavljevic L, et al. *Acta Oncol.* 2016;55(12):1425-1433; **27.** Takahashi H, et al. *Ann Surg Oncol.* 2011;18(4):1166-1174; **28.** Xu L, et al. *Stem Cell Res Ther.* 2019;10(1):219; **29.** Dow LE, et al. *Cell.* 2015;161(7):1539-1552; **30.** Fey SK, et al. *Cell Rep.* 2024;43(6):114270; **31.** Fumagalli A, et al. *Cell Stem Cell.* 2020;26(4):569-578; **32.** Ge Y, Fuchs E. *Nat Rev Genet.* 2018;19(5):311-325; **33.** Morgan RG, et al. *Br J Cancer.* 2015;112(4):714-719; **34.** Walker F, et al. *PLoS One.* 2011;6(7):e22733; **35.** High PC, et al. *Trends Cancer.* 2026:S2405-8033(2426)00037-00033; **36.** Okamoto Y, et al. *J Biol Chem.* 2020;295(14):4591-4603; **37.** Asfaha S, et al. *Cell Stem Cell.* 2015;16(6):627-638; **38.** Kobayashi S, et al. *Stem Cells.* 2012;30(12):2631-2644; **39.** Posey TA, et al. *Mol Cancer Ther.* 2023;22(5):667-678; **40.** Basak O, et al. *Cell Stem Cell.* 2017;20(2):177-190 e174; **41.** Conti S, et al. *Nat Commun.* 2024;15(1):3363; **42.** Shimokawa M, et al. *Nature.* 2017;545(7653):187-192; **43.** High PC, et al. *Cell Rep Med*. 2025;6(10):102363; **44.** Cao W, et al. *Nat Commun.* 2020;11(1):1961; **45.** Morgan RG, et al. *Br J Cancer.* 2018;118(4):558-565.

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