The Dynamic Role of LGR5 in EGFR-expressing Cancers

The Battle Against Epithelial Cancers

Pathogenic Plasticity

LGR5, The Moving Target

Merus closing in on cancer

Table of Contents

Epithelial cancers: common prevalence, dynamic biology

Epithelial cancers (eg, head & neck, colorectal, lung) are common and have a poor prognosis, despite an established treatment target (eg, epidermal growth factor receptor [EGFR])[1–3]

Head and neck cancer (H&N), colorectal cancer (CRC), non-small cell lung cancer, (NSCLC), and other epithelial cancers represent a major challenge in oncology. These cancers, collectively known as carcinomas, originate in the epithelial cells that line the surfaces and organs of the body.[4–7] Head and neck cancer, colorectal cancer, and non-small cell lung cancer are among the most prevalent. They share common risk factors (eg, tobacco, alcohol) and roughly half of patients experience recurrence following initial treatment.[5–8] In the United States alone, these 3 epithelial cancers account for about 450,000 new cases and 200,000 deaths annually,[9] underscoring the urgent need for new insights and dynamic treatment strategies.

FAST FACT Head and neck cancer, colorectal cancer, and non-small cell lung cancer account for ~450,000 new cases and 200,000 deaths each year in the U.S.[3]

Patients with these cancers often experience metastasis, which carries a poor prognosis: 5-year survival rates for metastatic (distant) disease are 36% for head and neck cancer, 17% for colorectal cancer, and 9% for lung cancer.[9] Systemic treatment options are available for these tumor types and EGFR (epidermal growth factor receptor) is a known therapeutic target.[1,2,10]

EGFR overexpression is typical of these cancers (ranging from 40% to 90%[11–13]), and helps drive tumor growth, invasion, and therapy resistance.[2,10,14,15] This makes EGFR an obvious target for epithelial cancers and there are EGFR-targeted therapies available. Monoclonal antibodies and tyrosine kinase inhibitors have become standard in many treatment algorithms. Unfortunately, these cancers routinely develop resistance to EGFR-targeted therapy over time.[1,2]

CLINICAL CONTEXT EGFR overexpression occurs in 40%–90% of these epithelial cancers.[11–13]

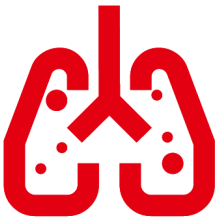
Head and Neck
(H&N)

>90% overexpress EGFR[11]

Colorectal
(CRC)

60%–80% overexpress EGFR[12]

Lung
(NSCLC)



40%–89% overexpress EGFR[13]

Plasticity is a critical hallmark of pathogenesis

Multiple hallmarks contribute to the pathogenesis of epithelial tumors and plasticity has emerged as a critical factor in cancer pathogenesis

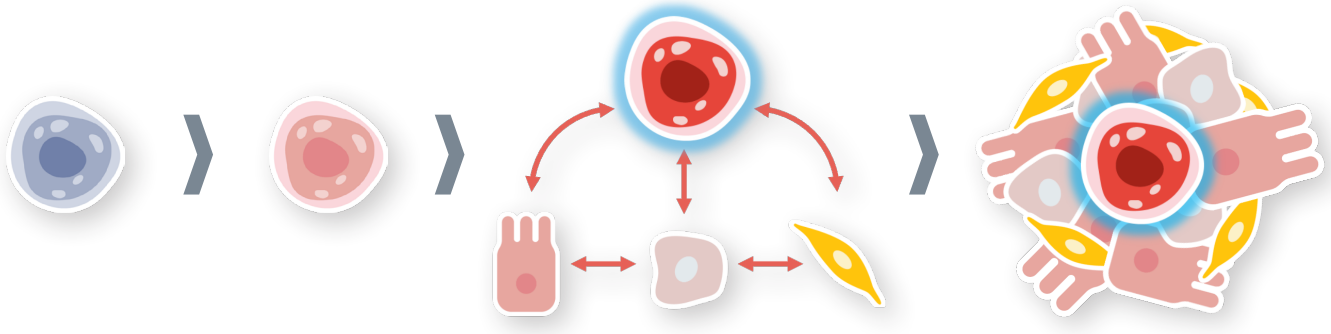
Cancer is not a static disease. It evolves, adapts, and resists as it progresses. This dynamism is driven by multiple hallmarks including the familiar (such as proliferation and metastasis), but also the newly understood hallmarks.[16–20] Plasticity, or a cell's ability to change type and behavior, is now recognized as a critical driver of cancer pathogenesis.[16]

Plasticity allows cancer cells to reprogram themselves using stem-cell–like abilities normally restricted to tissue regeneration.[16,18] Cancer cells with plasticity can self-renew, change identity, and transition between proliferative and dormant states—all of which can contribute to tumor growth, resistance, and metastasis.[16,21–24]

FAST FACT Plasticity allows cancer cells to 'reprogram' themselves, switching between proliferative/dormant and stationary/mobile.[16,21–24]

CLINICAL CONTEXT Cancer cells with plasticity can adapt to stress, resist targeted therapies, and seed new tumors in distant organs.[16,21–24]

Plasticity helps cancer survive. But it goes beyond that to help cancer thrive. Cancer cells with stem-like properties can adapt to stress in the tumor microenvironment, resist targeted therapies, and seed new tumors in distant organs.[16,21–24] This may complicate treatment and contribute to poor outcomes. Cancers that initially respond to therapy may later recur or metastasize.[16,21–24]



Normal cell | **Cancer cell** | **Cancer cell with plasticity** (stem-cell–like capabilities) | **Tumor expansion** (heterogeneous cell mass)

Plasticity makes treatment resistance possible

Plasticity, in the form of epithelial–mesenchymal transition, is an established resistance mechanism for EGFR-targeted therapy[25,26]

Although EGFR overexpression is a well-established driver of cancer progression, targeting EGFR itself can result in resistance after initial response.[2,16–18] One of the most well-known mechanisms of resistance is epithelial–mesenchymal transition (EMT), a form of plasticity that can make cancer cells nonresponsive to EGFR-targeted therapy.[25,26]

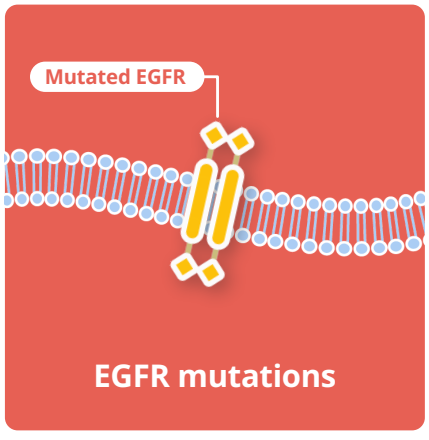
FAST FACT Epithelial–mesenchymal transition is a process that allows epithelial cancer cells to lose their stationary traits to instead become more mobile.[16]

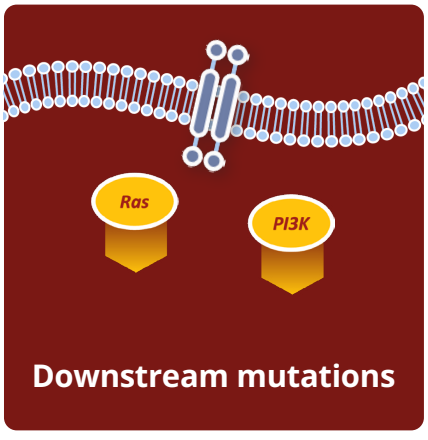
CLINICAL CONTEXT Epithelial–mesenchymal transition is an established resistance mechanism to EGFR-targeted therapy.[25,26]

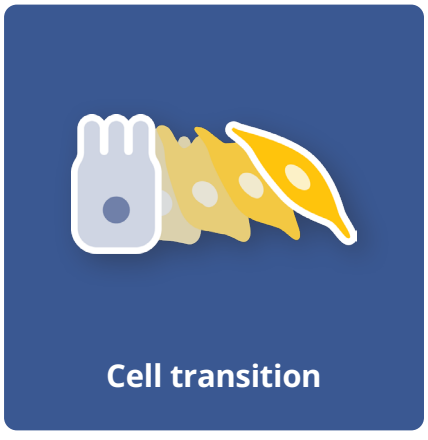
Epithelial–mesenchymal transition is a biological process that causes epithelial cells to lose some of their foundational characteristics (such as cell-to-cell adhesion), while simultaneously gaining mesenchymal capabilities (such as motility).[18] This transition allows cancer cells to escape the limitations of their original form and adopt a mobile, metastatic phenotype. Taking on a mesenchymal phenotype gives cancer cells the ability to evade treatments directed at epithelial cells, thereby becoming resistant to EGFR-targeted therapy.[25,26]

Other resistance mechanisms include EGFR kinase mutations (which interfere with drug-binding) and downstream mutations (which activate alternative signaling pathways).[25,26] These adaptations not only affect the response to EGFR inhibitors but also contribute to disease progression and metastasis.

Resistance mechanisms for EGFR-targeted therapy[25,26]



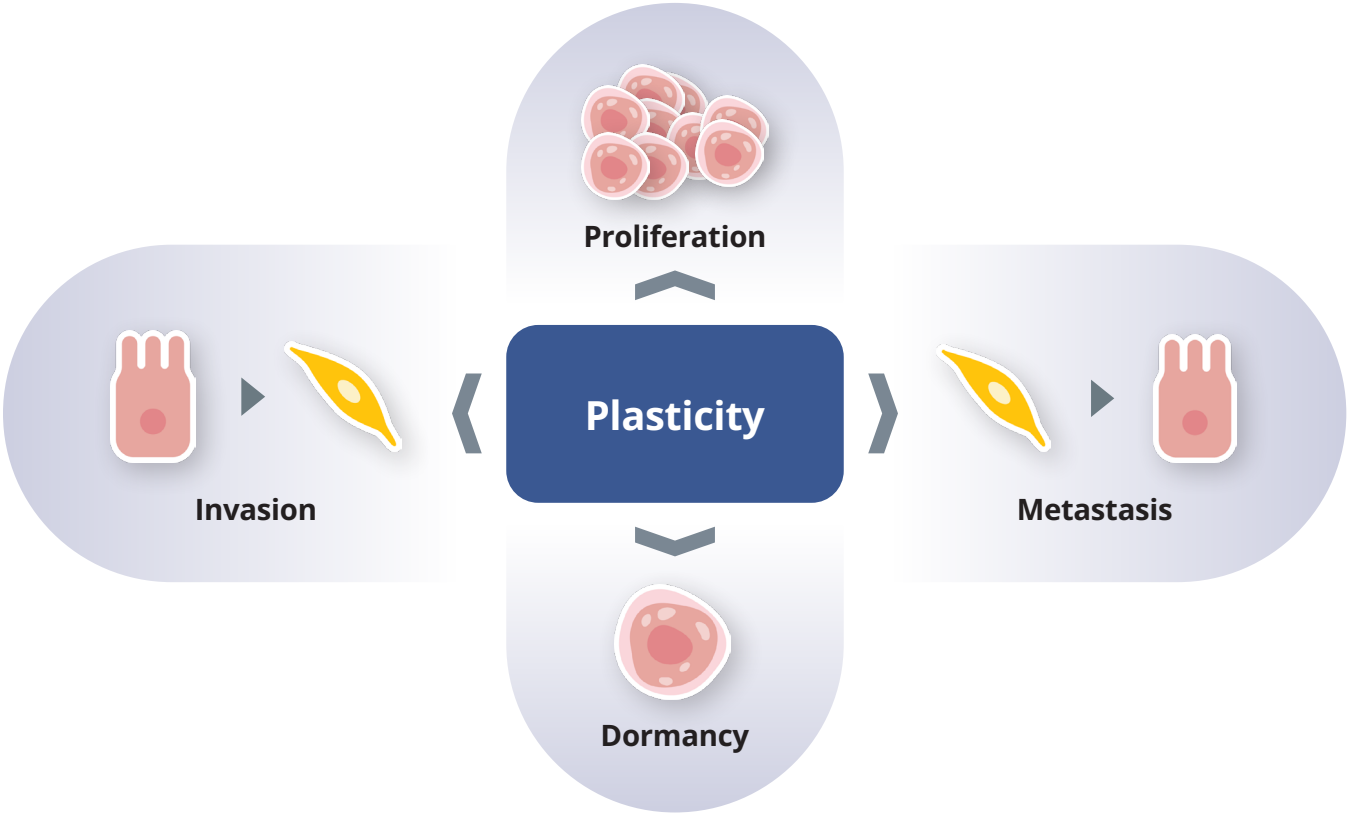




Plasticity regulates other cancer hallmarks

Plasticity drives epithelial cancer progression by orchestrating the action of other hallmarks[16]

Cellular plasticity is a dynamic capability; it commands and manipulates other cancer hallmarks, including proliferation, dormancy, invasion, and metastasis.[16] This allows cancer cells to shift between phenotypes and behaviors, which can help them survive, adapt, and thrive even under therapeutic pressure.



Plasticity allows epithelial cancer cells to transition between proliferative and dormant states, enabling resistance to cancer therapy. Further, plasticity can drive metastasis by exploiting proteins that support tissue repair and homeostasis.[16] Existing in a hybrid state, cancer cells with plasticity can have both epithelial and mesenchymal features, which is a hallmark of aggressive, treatment-resistant disease.[27] This dynamic identity enables them to migrate and re-establish tumors in distant organs.

Cancer cells with plasticity represent a small but powerful sub-population that can create tumors and drive metastasis.[22,28–32] These cells are both durable and enduring, making them uniquely suited to seed both primary and secondary tumors. In fact, epithelial cells with stem-like properties can be the cells of origin for many carcinomas, including ones that recur or metastasize.[30,33,34]

LGR5 is associated with an amplification of plasticity, which can be tumorigenic

LGR5 is associated with cell plasticity in epithelial tissue and cancer cells that acquire LGR5 expression can be the cell of origin for epithelial tumors[30,31,35,36]

Throughout the body are adult stem cells that replace dead or lost cells (eg, epithelial, blood, muscle, liver).[37,38] In epithelial tissue, adult stem cells are recognized by the expression of LGR5 (leucine-rich repeat-containing G-protein coupled receptor 5).[30,35,39] Normally, LGR5-positive adult stems cells are a small population in the basal crypt of the intestinal epithelium,[36,39–43] where they help replace epithelial cells lost to shedding.[39–43] LGR5 functions similarly in oral tissue where it supports tissue homeostasis,[44] and in lung tissue where it supports alveolar differentiation.[45,46]

- **Receptor for R-Spondins (RSPOs)[31,39,47,48]**
  - **RSPOs are stem-cell growth factors and potent signal enhancers[31,39,47,48]**
- **Expressed in adult epithelial stem cells[30,35,39]**
  - **LGR5-positive cells are self-renewing and long-lived (>6 months)[40–42,48,49]**

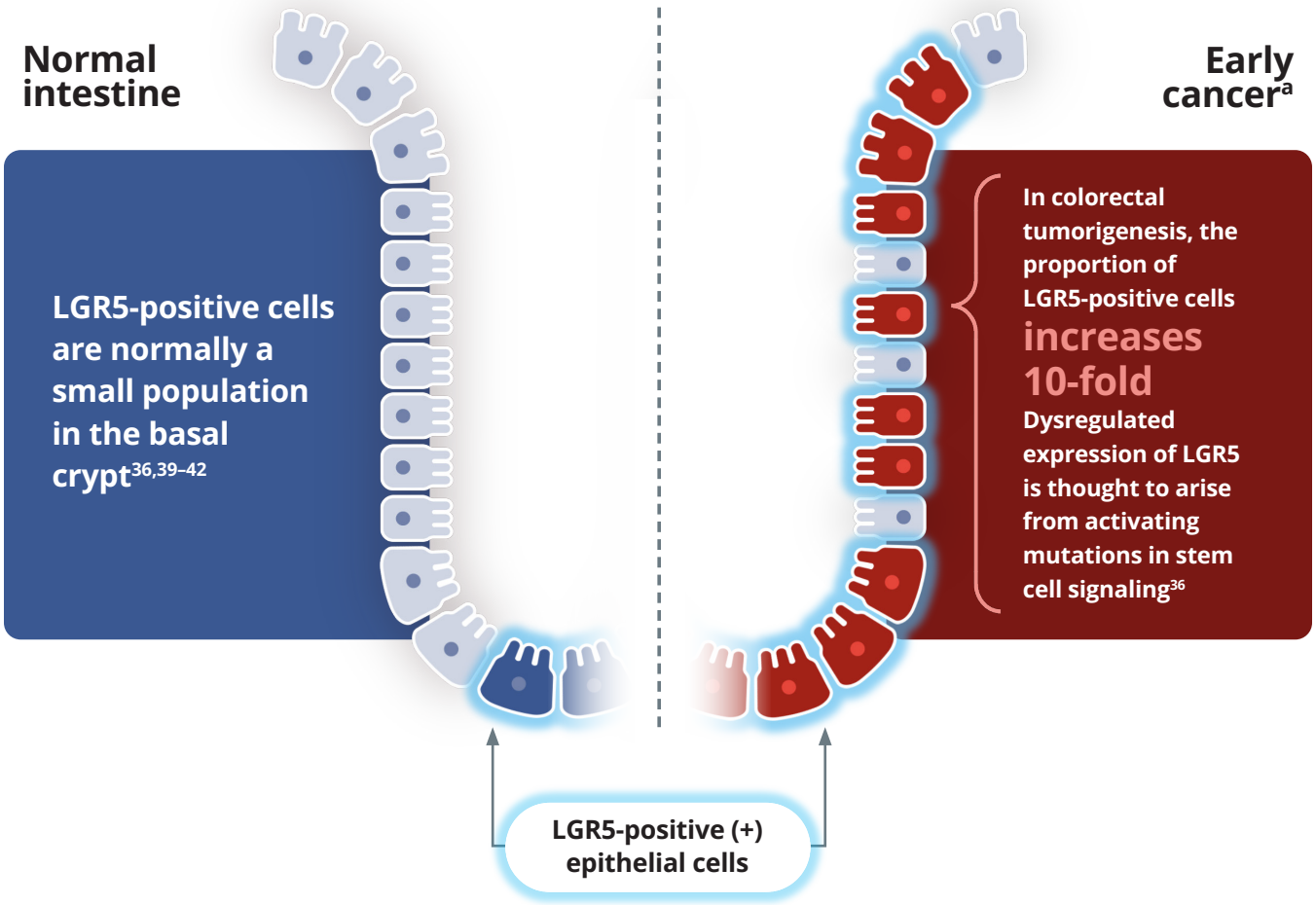
Adult stem cells in epithelial tissue (LGR5-positive):	When epithelial cancer cells hijack LGR5-positive expression:
Small population (eg, ~6% of intestinal crypt cells)[36,39–42]	Expanded expression (eg, ~70% of intestinal crypt cells)[36]
Maintains intestinal, oral, and lung tissue[30,45,46]	Accelerates stem cell signaling (Wnt/beta-catenin)[30,34,47]
Replaces cells lost to shedding[39–42]	Co-opts self-renewal for cancer progression[28–31,33–36]
Supports tissue homeostasis and wound repair[30,40,41]	Helps cancer grow, resist therapy, and spread[28–31,33–36]

What makes LGR5 such a powerful regulator of plasticity? LGR5 combines characteristics of longevity, potency, and signaling. It is a seven-transmembrane G-protein coupled receptor (GPCR) involved in stem-cell signaling and proliferation.[31,39,47,48] LGR5 is a receptor for R-Spondins (RSPOs), which are stem cell growth factors and potent signal enhancers.[30,35,39] LGR5-positive cells are self-renewing and long-lived (surviving for more than 6 months).[36,40–42,48,49]

LGR5-positive cells are normally a small population, comprising about 6% of the cells in the basal crypt of the intestinal epithelium.[36,39–42] However, in the initial stages of tumorigenesis, the percentage of these cells increases 10-fold (~70%), which can give cancer the ability to proliferate and differentiate.[30,31,36]

Overexpression of LGR5 has been observed across epithelial cancers, and has been associated with poor outcomes.[30,31,50–56] In colorectal cancer, LGR5 overexpression has been associated with a reduction in disease-free survival (1-year) as well as increases in the risk of recurrence (5-year) and liver metastasis.[51,52] In head and neck cancer, LGR5 overexpression is associated with lower overall survival (OS), and in non-small cell lung cancer, LGR5 expression is markedly elevated in tumor cells compared with healthy adjacent tissue.[53,55] LGR5 is a Wnt-target gene and activating mutations in the Wnt/beta-catenin signaling pathway are thought to drive dysregulated expression of LGR5.[36]

CLINICAL CONTEXT Overexpression of LGR5 has been associated with poor outcomes across epithelial cancers.[31,39,47,48]



[a]Adenomas and well- or moderately differentiated adenocarcinomas.[36]

LGR5 accelerates stem cell signaling and triggers epithelial–mesenchymal transition

LGR5 contributes to pathogenic plasticity by accelerating Wnt/β-catenin signaling and triggering epithelial–mesenchymal transition[30,34,47,57]

Wnt/β-catenin signaling

Wnt signaling is a driver of normal stem cell behavior and is a well-established driver of tumorigenesis. This pathway causes a protein called β-catenin to accumulate in the nucleus.[22,39,53] There it activates genes that promote proliferation and transformation, which cancer uses to drive progression, treatment resistance, and metastasis.[15,39,54,58–61]

FAST FACT LGR5 accelerates Wnt/β-catenin signaling, a pathway that can drive tumor growth, treatment resistance, and metastasis.[19,28,36,50]

LGR5 is thought to contribute to Wnt signaling by sequestering E3 ligases (enzymes that normally remove Wnt receptors from the cell surface).[a] This amplifies signal strength and sustains oncogenic activity.[31,34] Because LGR5 is itself a Wnt-target gene,[47] activating mutations in this pathway can unlock LGR5 expression.[36]

Epithelial–mesenchymal transition

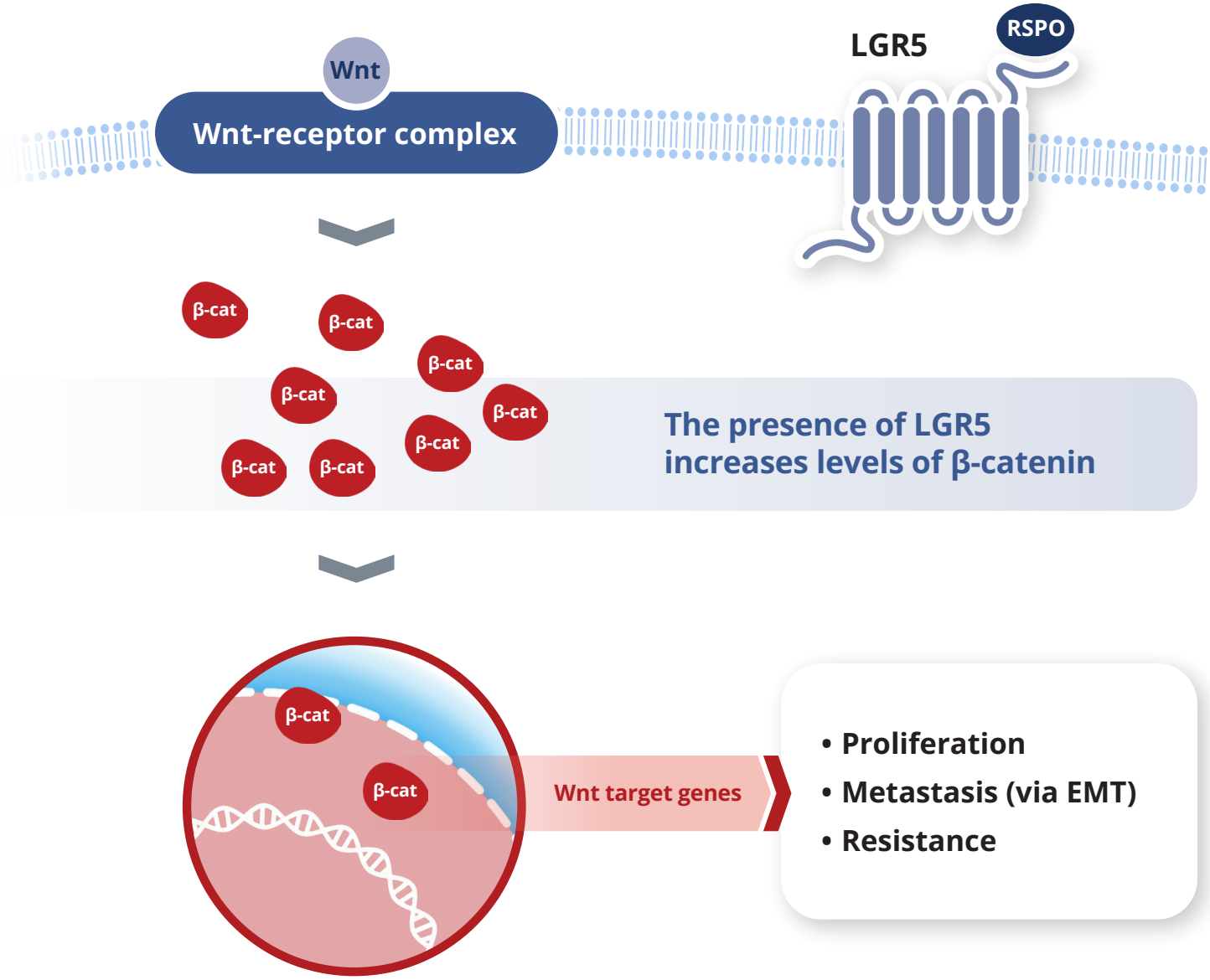
Wnt signaling drives metastasis through epithelial–mesenchymal transition, a process that allows epithelial cancer cells to lose their normal characteristics (such as cell adhesion) and take on mesenchymal traits (such as motility).[50,53,62] Acceleration of Wnt signaling induces epithelial–mesenchymal transition by upregulating transcription factors that control cell transformation.[39,53,63,64] With this transition, cancer cells can leave the primary tumor site and invade distant tissues.[22,39,53] Epithelial–mesenchymal transition associated transcription factors are upregulated in response to Wnt signaling and correlate with LGR5 expression.[39,53,63,64]

TRANSLATIONAL CONTEXT Wnt signaling drives epithelial–mesenchymal transition, allowing cancer cells to leave the tumor and form metastases in other areas of the body.[22,39,53]

When cancer cells reach a new environment, they undergo mesenchymal–epithelial transition (MET), the complementary process that restores epithelial characteristics and enables initiation of metastatic epithelial tumors.[24,65]

The interplay between LGR5, Wnt/β-catenin signaling, and epithelial–mesenchymal transition/mesenchymal–epithelial transition empowers tumor cells to invade other tissues and create new tumors.[53,54,63,66]

[a]This evidence is based on the LGR family of proteins since direct evidence for LGR5 is lacking.


Wnt
Wnt-receptor complex
LGR5
RSPO
β-cat
β-cat
β-cat
β-cat
β-cat
β-cat
β-cat
β-cat
The presence of LGR5 increases levels of β-catenin
β-cat
β-cat
Wnt target genes
• Proliferation
• Metastasis (via EMT)
• Resistance

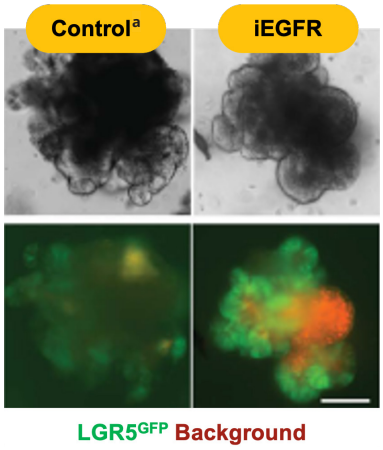
Therapy directed at EGFR can boost LGR5 expression

Preclinical data show that treatment with EGFR-targeted therapy increased expression of LGR5[23,42,67,68]

Multiple independent studies have shown that treatment with EGFR-targeted agents increased LGR5 expression in tumor cell models (mouse and human). This has been observed using both an EGFR-targeted antibody,[23,67] as well as a receptor tyrosine kinase inhibitor (RTKi) against EGFR.[42]

Increased expression of LGR5 after treatment with an EGFR RTK inhibitor (iEGFR)[42]

(mouse intestinal organoid models)

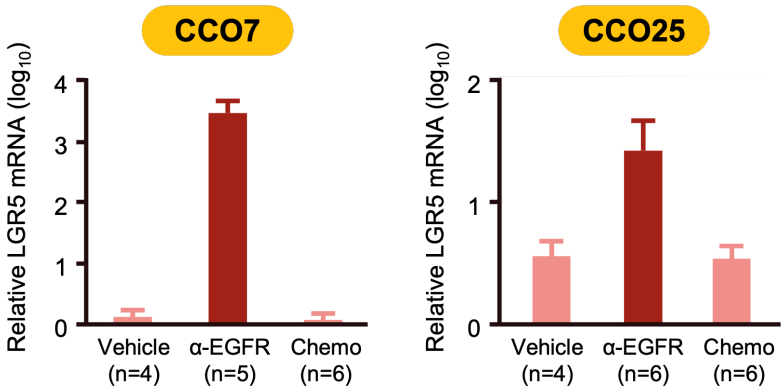


Reprinted from Basak O et al. Induced quiescence of Lgr5+ stem cells in intestinal organoids enables differentiation of hormone-producing enteroendocrine cells. *Cell Stem Cell*. 2017;20(2):177-190.e4, Copyright 2017, with permission from Elsevier.

[a]Epidermal growth factor, Noggin, and R-spondin-1 (ENR).

Increased expression of LGR5 after treatment with an anti-EGFR monoclonal antibody[23]

(human colon cancer organoids)



Reprinted from Shimokawa M et al. Visualization and targeting of LGR5+ human colon cancer stem cells. *Nature*. 2017;545(7653):187-192, Copyright 2017, with permission from Springer Nature.

Pathogenic plasticity in action

Epithelial cancers treated with EGFR-targeted therapy can develop resistance by undergoing epithelial-mesenchymal transition.[69–72] Interestingly, this cell transition is also known to result in the silencing of LGR5 expression,[35,73–75] suggesting the possibility of a deadly dynamic between LGR5 and resistance to EGFR-targeted therapy.

CLINICAL CONTEXT EGFR-targeted therapy can increase LGR5 expression, but transitioning from an epithelial to mesenchymal cell type can result in LGR5 silencing and EGFR therapy resistance.[28,29,35,73–75]

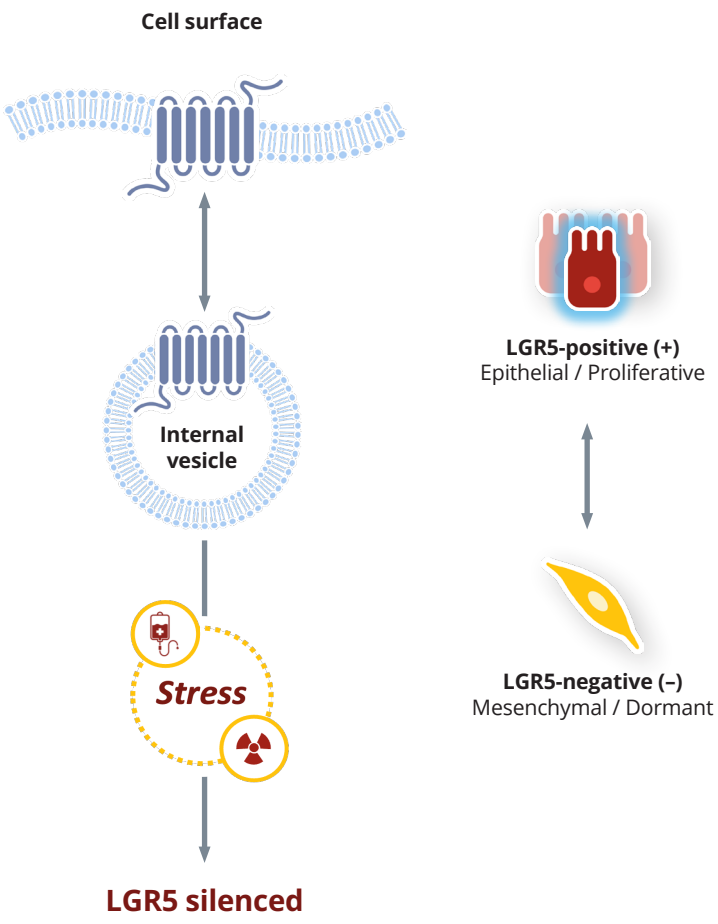
Is there a deadly dynamic between LGR5 and resistance to EGFR-targeted therapy?

Cancer cells change LGR5 expression to regulate disease progression

Changes in LGR5 expression allow cancer cells to resist treatment and metastasize[35,73–76]

Epithelial cancer cells are able to reversibly change LGR5 expression to resist treatment and metastasize.[35,73–76] This is possible because LGR5 is constantly internalized and replaced at the cell surface, allowing cancer cells to respond to changes in the tumor microenvironment.[47,77–79] When cells are stressed (eg, cancer treatment, nutrient deprivation) they silence LGR5 expression and surface localization of LGR5 is reduced.[77,78] This pauses proliferation, pushing cancer cells into a dormant, treatment-resistant state or a phenotype capable of migration and metastasis (mesenchymal).[29,74,76–78]

Switching between LGR5-positive and LGR5-negative states gives epithelial cancer cells the ability to change both phenotype and behavior: when cells are LGR5-positive, they are epithelial and proliferative; when cells switch to LGR5-negative, they are dormant with metastatic potential.This transition helps cancer cells survive therapy and spread throughout the body.[35,73–75]



Epithelial cancer cells with plasticity[35,36,39–42]	Epithelial cancer cells with plasticity under stress[29,74,76–78]
LGR5-positive	LGR5-negative
Tumor initiating	Mobile
Proliferative	Dormant

LGR5 has emerged as a compelling therapeutic target with dynamic properties

Because LGR5 is a dynamic protein, developing an effective therapeutic strategy around it may require the integration of other targets[23,28,31,50,80]

The expression of LGR5 fluctuates during cancer progression. This dynamism makes LGR5 a powerful regulator of cancer and a challenging target to address.[66,73,74]

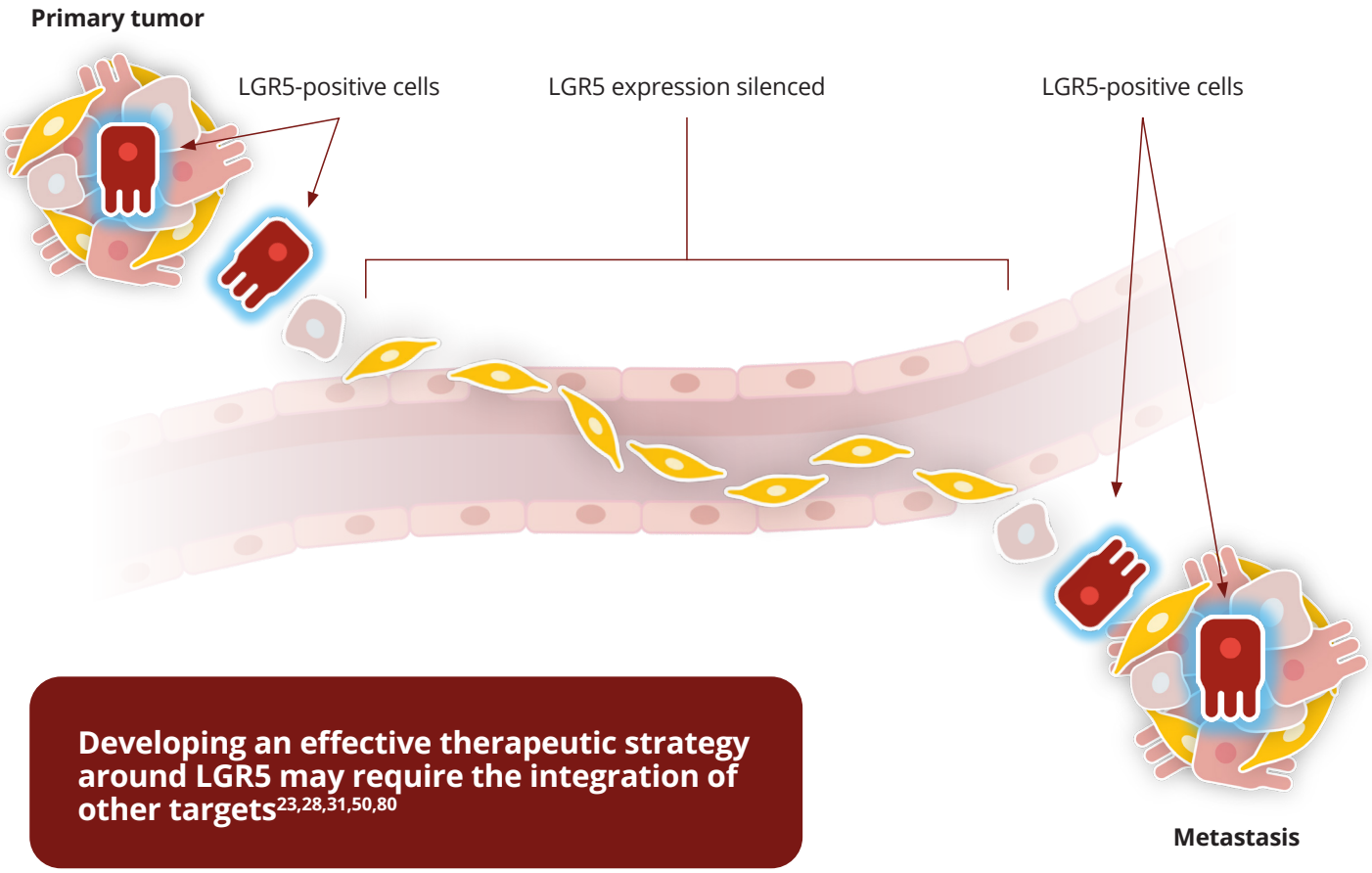
FAST FACT LGR5 expression can turn on and off in cancer cells. When it is "on," cells multiply. When it is "off," cells travel, hide, and then re-emerge.[35,73–75] These on/off dynamics occur during epithelial-mesenchymal transition, which is a resistance mechanism for EGFR-targeted therapy[25,26,66,74]

During metastasis, cancer cells strategically silence LGR5 expression, shedding their proliferative identity and adopting a mobile, mesenchymal-like phenotype.[66,74] This transition allows them to evade therapy, survive in circulation, and infiltrate distant tissues.[66,74]

After establishing a secondary tumor site, the cells reactivate LGR5 expression to restore epithelial traits and enable tumor cell proliferation.[66,74] The same is true when cancer cells expressing LGR5 are treated with anti-cancer treatment; expression is silenced temporarily and then reactivated.[29,73,76] This cycle of silencing and reactivation defines the plasticity that supports treatment resistance and disease progression.

Because LGR5 expression is dynamic, approaches that target it alone may not be effective for long-term control of epithelial cancers. Successfully using LGR5 as a therapeutic target may require the inclusion of other approaches or pathways.[23,28,31,50,80]

LGR5 is a moving target



Developing an effective therapeutic strategy around LGR5 may require the integration of other targets[23,28,31,50,80]

References

1. Kobayashi, K. Primary resistance to EGFR tyrosine kinase inhibitors (TKIs): contexts and comparisons in EGFR-mutated lung cancer. *J Respir*. 2023;3:223-236.
2. Halder S, Basu S, Lall SP, Ganti AK, Batra SK, Seshacharyulu P. Targeting the EGFR signaling pathway in cancer therapy: What's new in 2023? *Expert Opin Ther Targets*. 2023;27(4-5):305-324.
3. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. *CA Cancer J Clin*. 2025;75(1):10-45.
4. National Cancer Institute. Epithelial tissue. https://training.seer.cancer.gov/anatomy/cells_tissues_membranes/tissues/epithelial.html. Accessed September 2025.
5. Ionna F, Bossi P, Guida A, et al. Recurrent/metastatic squamous cell carcinoma of the head and neck: a big and intriguing challenge which may be resolved by integrated treatments combining locoregional and systemic therapies. *Cancers (Basel)*. 2021;13(10).
6. Kanwar SS, Poolla A, Majumdar AP. Regulation of colon cancer recurrence and development of therapeutic strategies. *World J Gastrointest Pathophysiol*. 2012;3(1):1-9.
7. Tahayneh K, Idkedek M, Abu Akar F. NSCLC: current evidence on its pathogenesis, integrated treatment, and future perspectives. *J Clin Med*. 2025;14(3).
8. van Zutphen M, Kampman E, Giovannucci EL, van Duijnhoven FJB. Lifestyle after colorectal cancer diagnosis in relation to survival and recurrence: a review of the literature. *Curr Colorectal Cancer Rep*. 2017;13(5):370-401.
9. SEER Cancer Statistics Explorer Network. 5-year Survival Rates (2015-2021). Available from: https://seer.cancer.gov/statistics-network/explorer/. Accessed September 2025.
10. London M, Gallo E. Epidermal growth factor receptor (EGFR) involvement in epithelial-derived cancers and its current antibody-based immunotherapies. *Cell Biol Int*. 2020;44(6):1267-1282.
11. Rehmani HS, Issaeva N. EGFR in head and neck squamous cell carcinoma: exploring possibilities of novel drug combinations. *Ann Transl Med*. 2020;8(13):813.
12. Pabla B, Bissonnette M, Konda VJ. Colon cancer and the epidermal growth factor receptor: Current treatment paradigms, the importance of diet, and the role of chemoprevention.World J Clin Oncol. 2015;6(5):133-141.
13. Prabhakar CN. Epidermal growth factor receptor in non-small cell lung cancer. *Transl Lung Cancer Res*. 2015;4(2):110-118.
14. Xu MJ, Johnson DE, Grandis JR. EGFR-targeted therapies in the post-genomic era. *Cancer Metastasis Rev*. 2017;36(3):463-473.
15. Liu B, Zhou H, Tan L, Siu KTH, Guan XY. Exploring treatment options in cancer: tumor treatment strategies. *Signal Transduct Target Ther*. 2024;9(1):175.
16. Hanahan D. Hallmarks of cancer: new dimensions. *Cancer Discov*. 2022;12(1):31-46.
17. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646-674.
18. Li J, Ma X, Chakravarti D, Shalapour S, DePinho RA. Genetic and biological hallmarks of colorectal cancer. *Genes Dev*. 2021;35(11-12):787-820.
19. Makitie AA, Almangush A, Rodrigo JP, Ferlito A, Leivo I. Hallmarks of cancer: tumor budding as a sign of invasion and metastasis in head and neck cancer. *Head Neck*. 2019;41(10):3712-3718.
20. Song Y, Wang Y, Guan A, et al. Footprints: stamping hallmarks of lung cancer with patient-derived models, from molecular mechanisms to clinical translation. *Front Bioeng Biotechnol*. 2023;11:1132940.
21. Cortina C, Turon G, Stork D, et al. A genome editing approach to study cancer stem cells in human tumors. *EMBO Mol Med*. 2017;9(7):869-879.
22. Major AG, Pitty LP, Farah CS. Cancer stem cell markers in head and neck squamous cell carcinoma. Stem Cells Int. 2013;2013:319489.
23. Shimokawa M, Ohta Y, Nishikori S, et al. Visualization and targeting of LGR5(+) human colon cancer stem cells. *Nature*. 2017;545(7653):187-192.
24. Xu Q, Zhang Q, Ishida Y, et al. EGF induces epithelial-mesenchymal transition and cancer stem-like cell properties in human oral cancer cells via promoting Warburg effect. *Oncotarget*. 2017;8(6):9557-9571.
25. Chhouri H, Alexandre D, Grumolato L. Mechanisms of acquired resistance and tolerance to EGFR targeted therapy in non-small cell lung cancer. *Cancers (Basel)*. 2023;15(2).
26. Zhou J, Ji Q, Li Q. Resistance to anti-EGFR therapies in metastatic colorectal cancer: underlying mechanisms and reversal strategies. *J Exp Clin Cancer Res*. 2021;40(1):328.
27. Thompson EW, Redfern AD, Brabletz S, et al. EMT and cancer: what clinicians should know. *Nat Rev Clin Oncol*. 2025;22(10):711-713.
28. Cao W, Li M, Liu J, et al. LGR5 marks targetable tumor-initiating cells in mouse liver cancer. *Nat Commun*. 2020;11(1):1961.
29. Kobayashi S, Yamada-Okabe H, Suzuki M, et al. LGR5-positive colon cancer stem cells interconvert with drug-resistant LGR5-negative cells and are capable of tumor reconstitution. *Stem Cells*. 2012;30(12):2631-2644.
30. Leung C, Tan SH, Barker N. Recent advances in Lgr5(+) stem cell research. *Trends Cell Biol*. 2018;28(5):380-391.
31. Morgan RG, Mortensson E, Williams AC. Targeting LGR5 in colorectal cancer: therapeutic gold or too plastic? *Br J Cancer*. 2018;118(11):1410-1418.
32. Quiroga M, Rodriguez-Alonso A, Alfonsin G, et al. Protein degradation by E3 ubiquitin ligases in cancer stem cells. *Cancers (Basel)*. 2022;14(4):900.

33. Barker N, Ridgway RA, van Es JH, et al. Crypt stem cells as the cells-of-origin of intestinal cancer. *Nature*. 2009;457(7229):608-611.
34. Hirsch D, Barker N, McNeil N, et al. LGR5 positivity defines stem-like cells in colorectal cancer. *Carcinogenesis*. 2014;35(4):849-858.
35. Ge Y, Fuchs E. Stretching the limits: from homeostasis to stem cell plasticity in wound healing and cancer. *Nat Rev Genet*. 2018;19(5):311-325.
36. Martin ML, Zeng Z, Adileh M, et al. Logarithmic expansion of LGR5(+) cells in human colorectal cancer. *Cell Signal*. 2018;42:97-105.
37. National Institutes of Health. Stem cell basics. https://stemcells. nih. gov/info/basics/stc-basics. Accessed March 2025.
38. Brunet A, Goodell MA, Rando TA. Ageing and rejuvenation of tissue stem cells and their niches. *Nat Rev Mol Cell Biol*. 2023;24(1):45-62.
39. de Lau W, Peng WC, Gros P, Clevers H. The R-spondin/Lgr5/Rnf43 module: regulator of Wnt signal strength. *Genes Dev*. 2014;28(4):305-316.
40. Barker N, Huch M, Kujala P, et al. Lgr5(+ve) stem cells drive self-renewal in the stomach and build long-lived gastric units in vitro. *Cell Stem Cell*. 2010;6(1):25-36.
41. Barker N, van Es JH, Kuipers J, et al. Identification of stem cells in small intestine and colon by marker gene Lgr5. *Nature*. 2007;449(7165):1003-1007.
42. Basak O, Beumer J, Wiebrands K, Seno H, van Oudenaarden A, Clevers H. Induced quiescence of Lgr5+ stem cells in intestinal organoids enables differentiation of hormone-producing enteroendocrine cells. *Cell Stem Cell*. 2017;20(2):177-190. e174.
43. Basnayake B, Leo P, Rao S, et al. Head and neck cancer patient-derived tumouroid cultures: opportunities and challenges. *Br J Cancer*. 2023;128(10):1807-1818.
44. Boddupally K, Wang G, Chen Y, Kobielak A. Lgr5 marks neural crest derived multipotent oral stromal stem cells. *Stem Cells*. 2016;34(3):720-731.
45. Zhang X, Xu M, Su S, et al. Lgr5-positive cells in the lung and their clinical significance in patients with lung adenocarcinoma. *Mol Clin Oncol*. 2016;5(2):283-288.
46. Zhang YQ, Li P, Zhang FQ, Sun SJ, Cao YG. Lgr5 regulates the regeneration of lesioned nasal respiratory epithelium. *Biochem Biophys Res Commun*. 2016;481(3-4):195-200.
47. Carmon KS, Lin Q, Gong X, Thomas A, Liu Q. LGR5 interacts and cointernalizes with Wnt receptors to modulate Wnt/beta-catenin signaling. *Mol Cell Biol*. 2012;32(11):2054-2064.
48. Koo BK, Clevers H. Stem cells marked by the R-spondin receptor LGR5. *Gastroenterology*. 2014;147(2):289-302.
49. Snippert HJ, van der Flier LG, Sato T, et al. Intestinal crypt homeostasis results from neutral competition between symmetrically dividing Lgr5 stem cells. *Cell*. 2010;143(1):134-144.
50. Xu L, Lin W, Wen L, Li G. Lgr5 in cancer biology: functional identification of Lgr5 in cancer progression and potential opportunities for novel therapy. *Stem Cell Res Ther*. 2019;10(1):219.
51. Takahashi H, Ishii H, Nishida N, et al. Significance of Lgr5(+ve) cancer stem cells in the colon and rectum. *Ann Surg Oncol*. 2011;18(4):1166-1174.
52. Stanisavljevic L, Myklebust MP, Leh S, Dahl O. LGR5 and CD133 as prognostic and predictive markers for fluoropyrimidine-based adjuvant chemotherapy in colorectal cancer. *Acta Oncol*. 2016;55(12):1425-1433.
53. Rot S, Kaune T, Taubert H, et al. Prognostic impact of mRNA levels of LGR5 transcript variants in OSCC patients. *BMC Cancer*. 2019;19(1):155.
54. Zhu Z, Yu S, Niu K, Wang P. LGR5 promotes invasion and migration by regulating YAP activity in hypopharyngeal squamous cell carcinoma cells under inflammatory condition. *PLoS One*. 2022;17(10):e0275679.
55. Gao F, Xu JC, You XR, et al. The biological functions of LGR5 in promoting non-small cell lung cancer progression. *Transl Cancer Res*. 2019;8(1):203-211.
56. Mueller N, de la Roche MA, de la Roche M. Insights from the bottom-up development of LGR5-targeting immunotherapeutics. *Immunother Adv*. 2025;5(1):ltaf017.
57. Novellasdemunt L, Kucharska A, Jamieson C, et al. NEDD4 and NEDD4L regulate Wnt signalling and intestinal stem cell priming by degrading LGR5 receptor. *EMBO J*. 2020;39(3):e102771.
58. Patel S, Alam A, Pant R, Chattopadhyay S. Wnt signaling and its significance within the tumor microenvironment: novel therapeutic insights. *Front Immunol*. 2019;10:2872.
59. Zhu GX, Gao D, Shao ZZ, Chen L, Ding WJ, Yu QF. Wnt/beta catenin signaling: causes and treatment targets of drug resistance in colorectal cancer (Review). *Mol Med Rep*. 2021;23(2).
60. Liu XS, Lin XK, Mei Y, et al. Regulatory T cells promote overexpression of Lgr5 on gastric cancer cells via TGF-beta1 and confer poor prognosis in gastric cancer. *Front Immunol*. 2019;10:1741.
61. Liu J, Xiao Q, Xiao J, et al. Wnt/beta-catenin signalling: function, biological mechanisms, and therapeutic opportunities. *Signal Transduct Target Ther*. 2022;7(1):3.
62. de Sousa e Melo F, Kurtova AV, Harnoss JM, et al. A distinct role for Lgr5(+) stem cells in primary and metastatic colon cancer. *Nature*. 2017;543(7647):676-680.
63. Li F, Song X, Li X, et al. Lgr5 maintains stemness and regulates cell property in nasopharyngeal carcinoma through Wnt/beta-catenin signaling pathway. *Stem Cell Res*. 2020;47:101916.
64. Sun L, Xing J, Zhou X, Song X, Gao S. Wnt/beta-catenin signalling, epithelial-mesenchymal transition and crosslink signalling in colorectal cancer cells. *Biomed Pharmacother*. 2024;175:116685.

65. Yao D, Dai C, Peng S. Mechanism of the mesenchymal-epithelial transition and its relationship with metastatic tumor formation. *Mol Cancer Res*. 2011;9(12):1608-1620.
66. Conti S, Venturini V, Canellas-Socias A, et al. Membrane to cortex attachment determines different mechanical phenotypes in LGR5+ and LGR5- colorectal cancer cells. *Nat Commun*. 2024;15(1):3363.
67. High PC, Liang Z, Guernsey-Biddle C, et al. Cetuximab increases LGR5 expression and augments LGR5-targeting antibody-drug conjugate efficacy in patient-derived colorectal cancer models. *bioRxiv*. 2025:2025. 06. 18. 660406.
68. Lupo B, Sassi F, Pinnelli M, et al. Colorectal cancer residual disease at maximal response to EGFR blockade displays a druggable Paneth cell-like phenotype. *Sci Transl Med*. 2020;12(555):eaax8313.
69. Schinke H, Shi E, Lin Z, et al. A transcriptomic map of EGFR-induced epithelial-to-mesenchymal transition identifies prognostic and therapeutic targets for head and neck cancer. *Mol Cancer*. 2022;21(1):178.
70. Clement MS, Gammelgaard KR, Nielsen AL, Sorensen BS. Epithelial-to-mesenchymal transition is a resistance mechanism to sequential MET-TKI treatment of MET-amplified EGFR-TKI resistant non-small cell lung cancer cells. *Transl Lung Cancer Res*. 2020;9(5):1904-1914.
71. Jakobsen KR, Demuth C, Sorensen BS, Nielsen AL. The role of epithelial to mesenchymal transition in resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer. *Transl Lung Cancer Res*. 2016;5(2):172-182.
72. Kagohara LT, Zamuner F, Davis-Marcisak EF, et al. Integrated single-cell and bulk gene expression and ATAC-seq reveals heterogeneity and early changes in pathways associated with resistance to cetuximab in HNSCC-sensitive cell lines. *Br J Cancer*. 2020;123(1):101-113.
73. Fey SK, Vaquero-Siguero N, Jackstadt R. Dark force rising: reawakening and targeting of fetal-like stem cells in colorectal cancer. *Cell Rep*. 2024;43(6):114270.
74. Fumagalli A, Oost KC, Kester L, et al. Plasticity of Lgr5-negative cancer cells drives metastasis in colorectal cancer. *Cell Stem Cell*. 2020;26(4):569-578 e567.
75. Walker F, Zhang HH, Odorizzi A, Burgess AW. LGR5 is a negative regulator of tumourigenicity, antagonizes Wnt signalling and regulates cell adhesion in colorectal cancer cell lines. *PLoS One*. 2011;6(7):e22733.
76. Posey TA, Jacob J, Parkhurst A, et al. Loss of LGR5 through therapy-induced downregulation or gene ablation is associated with resistance and enhanced MET-STAT3 signaling in colorectal cancer cells. *Mol Cancer Ther*. 2023;22(5):667-678.
77. Morgan RG, Molnar E, Jones RF, et al. Nutrient stress alters the glycosylation status of LGR5 resulting in reduced protein stability and membrane localisation in colorectal tumour cells: implications for targeting cancer stem cells. *Br J Cancer*. 2015;112(4):714-719.
78. Okamoto Y, Saito T, Tani Y, et al. The kinase PERK represses translation of the G-protein-coupled receptor LGR5 and receptor tyrosine kinase ERBB3 during ER stress in cancer cells. *J Biol Chem*. 2020;295(14):4591-4603.
79. Snyder JC, Rochelle LK, Lyerly HK, Caron MG, Barak LS. Constitutive internalization of the leucine-rich G protein-coupled receptor-5 (LGR5) to the trans-Golgi network. *J Biol Chem*. 2013;288(15):10286-10297.
80. Morgan RG, Mortensson E, Legge DN, et al. LGR5 expression is regulated by EGF in early colorectal adenomas and governs EGFR inhibitor sensitivity. *Br J Cancer*. 2018;118(4):558-565.

Key takeaways

Scan the code to learn more at
www.CancersWildCard.com

The Battle Against Epithelial Cancers

- Epithelial cancers (eg, head and neck, colorectal, lung) are common and have a poor prognosis, despite an established treatment target (eg, EGFR)[1–3]
- Multiple hallmarks contribute to the pathogenesis of epithelial tumors and plasticity has emerged as a critical factor in cancer pathogenesis[16]
- Plasticity, in the form of epithelial–mesenchymal transition, is an established resistance mechanism for EGFR-targeted therapy[25,26]

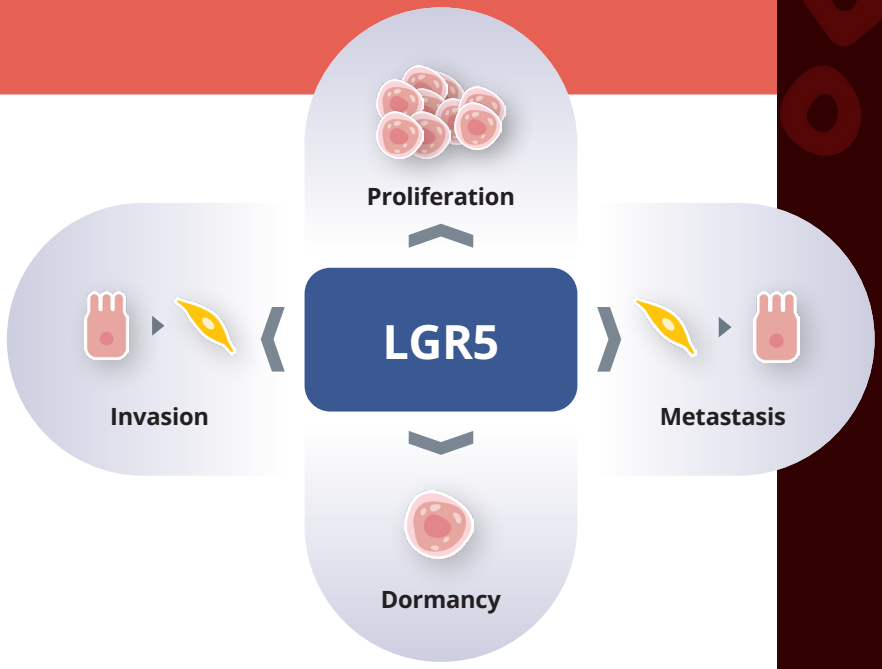
Pathogenic Plasticity

- Plasticity drives epithelial cancer progression—and does so by orchestrating other cancer hallmarks[16]
- LGR5 is an epithelial stem cell protein that enables plasticity, tumor initiation, and metastasis[30,31,35,36,39–42]
- LGR5 drives pathogenic plasticity by accelerating Wnt/β-catenin signaling and triggering epithelial–mesenchymal transition[30,34,47,57]

LGR5, The Moving Target

- EGFR-targeted therapy increased LGR5 expression,[23,42,67,68,a] but these effects may be silenced by epithelial–mesenchymal transition,[66,74] a known EGFR resistance mechanism[25,26]
- Fluctuations in LGR5 expression enable treatment resistance and metastasis[35,73–75]
- Because LGR5 expression can fluctuate, developing an effective therapy around it may require the integration of other targets or pathways[23,28,31,50,80]

[a]Based on preclinical data.



Merus