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A Two-Step Toward Personalized Therapies for Prostate Cancer

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Abstract

Identifying the dominant genetic alterations that drive tumorigenesis is essential for developing targeted cancer therapies. Recent work has demonstrated that prostate tumors can be stratified by dominant genetic alterations, such as chromosomal rearrangements involving ETS (Erythroblastosis virus E26 transformation-specific) family transcription factors or overexpression of *SPINK1*, a gene that encodes a secreted serine protease inhibitor. In this issue of *Science Translational Medicine*, Ateeq *et al.* provide evidence to support a rationale for targeting the SPINK1 protein in the *SPINK1*⁺/*ETS*[−] subset of prostate tumors and also describe a potential interaction of SPINK1 with epidermal growth factor receptor that could be an additional target for therapeutic intervention.

PERSONALIZED MEDICINE

The concept of “one-size-fits-all” therapeutics is becoming increasingly less relevant because any one therapy is unlikely to be effective for all individuals with a complex disease such as cancer. For the hundreds of thousands of men who are diagnosed with prostate cancer each year, their tumors do not all share the same molecular machinery, pathways, or targets. The goal of personalized medicine is to treat patients individually by targeting the pathways that are present or activated in that specific tumor. A major advance in personalized medicine has been the subclassification of tumor types according to histological features, molecular profiles, or dominant genetic alterations. In this issue of *Science Translational Medicine*, Ateeq *et al.* propose that combined therapy against SPINK1 and the receptor tyrosine kinase EGFR (epidermal growth factor receptor) might be effective in a subset of aggressive prostate tumors marked by overexpression of *SPINK1* (1).

Several noteworthy examples of successful tumor classification and targeted therapeutics are breast cancer, lymphoma, leukemia, and lung cancer, each of which has been divided into

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One-sentence summary: Therapeutic targeting of two proteins that drive tumorigenesis suggests personalized medicine is a possibility for prostate cancer.

several distinct subtypes of cancer. Within each subtype, many molecular targets are shared, and these targets can be specifically inhibited by using different types of therapeutics. For instance, the *HER2*⁺ subset of breast cancer is characterized by the expression of high concentrations of the receptor Her2 (ErbB2), which is the target of the therapeutic monoclonal antibody trastuzumab (Herceptin) (2). Monoclonal antibody treatments have been effective against proteins that are presented outside of the cell, such as trastuzumab in breast cancers and rituximab for B cell lymphomas that express CD20 (3). However, antibodies are not able to efficiently access intracellular proteins; small-molecule inhibitors have therefore been used to interfere with signaling networks inside of cells (Fig. 1). One of the many subtypes of leukemia, chronic myelogenous leukemia, is driven by BCR-ABL and can be treated with the small-molecule inhibitor imatinib (Gleevec) (4). Another important targeted therapy for patients who share molecular features is gefitinib for nonsmall-cell lung cancers with EGFR mutations (5). Such therapies are only effective when the overexpressed or mutated protein target is present in the tumor cell.

Although subclassification of tumors has been useful for treating several cancer types, attempts to stratify or cluster prostate cancers on the basis of histology or transcriptional profile have not been as successful. Instead, recent efforts have focused on subtyping prostate tumors for diagnostic purposes by using genomic classification. In a recent article in *Cancer Cell*, Taylor *et al.* divided prostate tumors into distinct groups on the basis of one genomic measurement: copy number variation. Patient data were clustered into six categories depending on the degree of copy number alterations. This variable alone was capable of predicting disease outcome (6). Although these findings do not directly lead to tailored therapies for a cluster of tumors, they suggest that tumor outcome can be predicted at an earlier stage. Chinnaiyan and colleagues have stratified tumors on the basis of the dominant genetic alteration, with the goal that each different subtype could be treated with a specific therapy. After identifying numerous chromosomal rearrangements involving *ETS* family transcription factors (7), Tomlins *et al.* have defined a distinct subtype of aggressive prostate cancers characterized by overexpression of *SPINK1* and lack of *ETS* rearrangements (*SPINK1*⁺/*ETS*⁻) (8). These studies lend support to the notion that a personalized medicine approach might be beneficial—or even necessary—for the treatment of prostate cancer. One can imagine a scenario in which prostate cancer patients are diagnosed on the basis of biopsy material, stratified into *ETS*⁺ tumors, *SPINK1*⁺ tumors, or other categories, and treated with specific therapies designed for the specific subtype. Ateeq *et al.* take the next step in this approach to identify *SPINK1* and EGFR as targets for the *SPINK1*⁺ subset of prostate tumors (1). Further studies are underway to address therapeutic targets specific to the *ETS*⁺ subset of prostate tumors.

NEW THINKING ON SPINK

SPINK1 is overexpressed in several cancers, and serves as a biomarker of poor prognosis in many tumors (9–11). In prostate cancer, *SPINK1* overexpression is correlated with increasing Gleason score—the disease grade obtained by histological analysis—disease recurrence, and poor prognosis (12, 13). The 22RV1 xenograft, an androgen-independent subline of prostate cancer cells originally obtained from a patient prostate tumor, represents an excellent model to investigate *SPINK1* function owing to naturally occurring *SPINK1* overexpression relative to benign epithelium. In addition to the *SPINK1*⁺ cancer xenograft, Ateeq *et al.* also used a benign immortalized prostate cell line (RWPE) for further functional investigation. *SPINK1* is an extracellular secreted protein; the authors therefore found that addition of recombinant *SPINK1* (rSPINK1) in the media could stimulate aggressive properties, such as proliferation and invasiveness, in benign and cancer cells of prostatic origin. Knockdown of *SPINK1* with short hairpin RNA (shRNA) in 22RV1 cells blocks proliferation and invasion in vitro and tumor formation in mice. These results indicate that

SPINK1 concentrations might control aggressive cell behavior and that targeting SPINK1 could be an effective therapeutic strategy for treating *SPINK1*⁺/*ETS*⁻ tumors.

Although knockdown was useful in culture, the technology to deliver small RNAs to cancer cells in vivo is in early stages of development. A clinical trial has used transferrin-coated nanoparticles to introduce small interfering RNA against the malignancy-associated protein RRM2 (ribonucleotide reductase M2) into melanoma cells that highly express the transferrin receptor (14). In this trial, the authors demonstrated mRNA cleavage and knockdown of RRM2 in a dose-dependent manner in cancer tissues. However, nanoparticles were heterogeneously distributed into tumors, and results varied among patients (14), suggesting that further developments are necessary before RNA interference has widespread applicability in cancer therapy. The most common strategy to deliver targeted therapies into tumor cells, including prostate cancer, is through small-molecule inhibitors (Fig. 1). For instance, the anti-androgen MDV3100 has been effective against castration-resistant prostate cancer cells driven by the androgen receptor (AR) (15). In contrast, monoclonal antibodies have been proven to access proteins found in the extracellular space and mediate anticancer effects (Fig. 1). Ateeq *et al.* found that monoclonal antibody treatment against SPINK1 could attenuate in vitro proliferation and invasion and in vivo tumor formation in the *SPINK1*⁺/*ETS*⁻ 22RV1 xenograft. This attenuation was not seen in *SPINK1*⁻ PC3 cancer cell xenografted mice, thus suggesting that monoclonal antibodies to SPINK1 might have a selective therapeutic effect against the *SPINK1*⁺ subset of prostate tumors.

SPINK1 AND EGFR

Because SPINK1 is a trypsin inhibitor, Ateeq *et al.* proposed that its function in cancer progression might be related to members of the trypsin family of proteases known to be present in benign and malignant prostate tissue (1). However, they found that the addition of rSPINK1 did not affect the expression of trypsin or prostate-specific antigen (PSA), a serine protease and the only confirmed biomarker for prostate cancer; these findings suggest that SPINK1 has direct influence on cell proliferation and invasiveness, independent of protease inhibitor activity (1). Ozaki *et al.* have proposed that SPINK1 spurs progression of pancreatic cancer cells through a direct interaction with EGFR, a mechanism that is unrelated to the SPINK1 trypsin inhibitor function (16). EGFR is a therapeutic target in several cancers, and its expression is found in a subset of prostate tumors (17, 18). SPINK1 and EGF, the EGFR ligand, share 50% amino acid homology and several structural similarities, and on the basis of immunoprecipitation experiments, Ateeq *et al.* have proposed a direct interaction between SPINK1 and EGFR in prostate cancer cells (1). In addition, SPINK1 can induce EGFR dimerization and phosphorylation (1), which indicates that SPINK1 functions at least in part to stimulate EGFR signaling in an autocrine loop (Fig. 1A). It has been proposed previously that SPINK1 competes with EGF (19), but it is unclear whether SPINK1 acts predominantly as a pseudo-ligand or as an allosteric effector of EGF binding to EGFR in the context of prostate cancer.

A monoclonal antibody to EGFR, cetuximab, has already been approved by the FDA (20). Ateeq *et al.* found that antibody-mediated blockage of EGFR can partially inhibit invasiveness in RWPE prostate cancer cells that have been stimulated with rSPINK1 in vitro. Interestingly, EGFR inhibition could diminish tumor-formation in *SPINK1*⁺ 22RV1 xenografted mice, without affecting cell proliferation (1). This effect was only observed in *SPINK1*⁺ 22RV1 cells, suggesting that EGFR could be a second therapeutic target specifically in this subset of prostate tumors. Combined targeted therapy has shown additional benefit over single therapies in experimental models of prostate (21) and other cancers (22). Ateeq *et al.* demonstrate that combined monoclonal antibody treatment that targeted both SPINK1 and EGFR was additive, causing a larger reduction in tumor

formation than either monoclonal antibody alone (1), thus providing further rationale for combined targeted therapy in prostate cancer (Fig. 1B).

These results suggest a potential treatment to diminish or slow tumorigenesis in *SPINK1*⁺/*ETS*⁻ cells. Nonetheless, because these experiments were mainly performed in the 22RV1 xenograft model it remains to be seen whether combined antibody treatment to *SPINK1* and EGFR is effective across a broad range of patient tumors. Although these data support *SPINK1* and EGFR targeting in *SPINK1*⁺ tumors, there may be additional genetic alterations that alter therapeutic effectiveness. Therefore, testing the effects of combined antibody therapy against a diverse group of tumors with varying genetics, in primary cells and xenografts, could help to define such underlying genetic alterations (such as *SPINK1*⁺, EGFR overexpression, or PTEN status) that determine susceptibility to treatment. An alternative approach to testing a wide range of tumors with varying genetics is to transform benign human prostate cells with defined genetic alterations and determine the susceptibility of the resulting tumors to treatment with single or combined antibodies. We have recently described a system to introduce oncogenes directly into naïve primary benign epithelial cells, transplant these cells into immune-deficient mice, and monitor tumor initiation and progression (23). Using this assay, it could be determined whether activation of certain pathways can predict sensitivity to *SPINK1* and EGFR antibody treatment.

UNCOVERING THE ROLE OF SPINK1

Although Ateeq *et al.* demonstrate diminution of tumor formation in vivo in a mouse xenograft model with *SPINK1* antibodies, the effect is not curative, suggesting that additional pathways must be inhibited to completely halt cancer progression. Furthermore, EGFR inhibition alone also was not sufficient to block cancer proliferation. Perhaps *SPINK1* acts as a ligand for other EGFR family receptors or other surface receptors highly expressed in prostate cancer cells, thus leading to downstream signaling that drives proliferation. Additional questions remain about *SPINK1* and its role in prostate cancer: Why are *SPINK1*⁺ tumors and *ETS*⁺ tumors mutually exclusive? Is the trypsin inhibitor function of *SPINK1* important for cancer pathogenesis, perhaps through a trypsin family member that has not yet been investigated? What causes *SPINK1* overexpression, if not genomic amplification? Is *SPINK1* overexpression an initiating event in prostate malignancy? Indeed, further studies are necessary to delineate the precise role and mechanism of *SPINK1* in the prostate.

To date, AR signaling remains the predominant therapeutic target for patients with advanced prostate cancer (15). The identification and validation of additional targets in advanced disease is extremely important. EGFR has been a candidate for therapy because high expression is observed in 18 to 40% of prostate cancers, and its expression correlates with high Gleason scores, high PSA concentrations, and disease recurrence (17, 18). However, disappointing results in trials of EGFR-targeted therapies for prostate cancer with gefitinib (24–26), lapatinib (27), or cetuximab (20) raise doubts about the importance of the EGFR signaling pathway for most prostate cancers. Ateeq *et al.* provide compelling justification for a carefully designed clinical trial that tests the effects of combined inhibition of EGFR and *SPINK1* in prostate tumors that display *SPINK1* overexpression and lack *ETS* rearrangements. Rather than declaring EGFR a poor target, we should consider that EGFR inhibition, in combination with other personalized and targeted therapies, might be an effective strategy for a defined subset of prostate cancer patients.

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REFERENCE AND NOTES

1. Ateeq B, Tomlins SA, Laxman B, Asangani IA, Cao Q, Cao X, Li Y, Wang X, Feng FY, Pienta KJ, Varambally S, Chinnaiyan AM. Therapeutic targeting of SPINK1-positive prostate cancer. *Science Translational Medicine*. 2011; 3:72ra17.
2. Goldenberg MM. Trastuzumab, a recombinant DNA-derived humanized monoclonal antibody, a novel agent for the treatment of metastatic breast cancer. *Clin. Ther.* 1999; 21:309–318. doi: 10.1016/S0149-2918(00)88288-0 Medline. [PubMed: 10211534]
3. Anderson DR, Grillo-López A, Varns C, Chambers KS, Hanna N. Targeted anti-cancer therapy using rituximab, a chimaeric anti-CD20 antibody (IDECC2B8) in the treatment of non-Hodgkin's B-cell lymphoma. *Biochem. Soc. Trans.* 1997; 25:705–708. Medline. [PubMed: 9191187]
4. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, Zimmermann J, Lydon NB. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat. Med.* 1996; 2:561–566. doi:10.1038/nm0596-561 Medline. [PubMed: 8616716]
5. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, Haber DA. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N. Engl. J. Med.* 2004; 350:2129–2139. doi:10.1056/NEJMoa040938 Medline. [PubMed: 15118073]
6. Taylor BS, Schultz N, Hieronymus H, Gopalan A, Xiao Y, Carver BS, Arora VK, Kaushik P, Cerami E, Reva B, Antipin Y, Mitsiades N, Landers T, Dolgalev I, Major JE, Wilson M, Socci ND, Lash AE, Heguy A, Eastham JA, Scher HI, Reuter VE, Scardino PT, Sander C, Sawyers CL, Gerald WL. Integrative genomic profiling of human prostate cancer. *Cancer Cell*. 2010; 18:11–22. doi: 10.1016/j.ccr.2010.05.026 Medline. [PubMed: 20579941]
7. Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R, Sun XW, Varambally S, Cao X, Tchinda J, Kuefer R, Lee C, Montie JE, Shah RB, Pienta KJ, Rubin MA, Chinnaiyan AM. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. *Science*. 2005; 310:644–648. doi:10.1126/science.1117679 Medline. [PubMed: 16254181]
8. Tomlins SA, Rhodes DR, Yu J, Varambally S, Mehra R, Perner S, Demichelis F, Helgeson BE, Laxman B, Morris DS, Cao Q, Cao X, Andrén O, Fall K, Johnson L, Wei JT, Shah RB, Al-Ahmadie H, Eastham JA, Eggener SE, Fine SW, Hotakainen K, Stenman UH, Tsodikov A, Gerald WL, Lilja H, Reuter VE, Kantoff PW, Scardino PT, Rubin MA, Bjartell AS, Chinnaiyan AM. The role of SPINK1 in ETS rearrangement-negative prostate cancers. *Cancer Cell*. 2008; 13:519–528. doi:10.1016/j.ccr.2008.04.016 Medline. [PubMed: 18538735]
9. Gaber A, Johansson M, Stenman UH, Hotakainen K, Pontén F, Glimelius B, Bjartell A, Jirstrom K, Birgisson H. High expression of tumour-associated trypsin inhibitor correlates with liver metastasis and poor prognosis in colorectal cancer. *Br. J. Cancer*. 2009; 100:1540–1548. doi:10.1038/sj.bjc.6605047 Medline. [PubMed: 19384300]
10. Lee YC, Pan HW, Peng SY, Lai PL, Kuo WS, Ou YH, Hsu HC. Overexpression of tumour-associated trypsin inhibitor (TATI) enhances tumour growth and is associated with portal vein invasion, early recurrence and a stage-independent prognostic factor of hepatocellular carcinoma. *Eur. J. Cancer*. 2007; 43:736–744. doi:10.1016/j.ejca.2006.11.020 Medline. [PubMed: 17267202]
11. Stenman UH. Tumor-associated trypsin inhibitor. *Clin. Chem.* 2002; 48:1206–1209. Medline. [PubMed: 12142374]
12. Paju A, Hotakainen K, Cao Y, Laurila T, Gadaleanu V, Hemminki A, Stenman UH, Bjartell A. Increased expression of tumor-associated trypsin inhibitor, TATI, in prostate cancer and in androgen-independent 22Rv1 cells. *Eur. Urol.* 2007; 52:1670–1679. doi:10.1016/j.eururo.2007.01.096 Medline. [PubMed: 17306443]

13. Leinonen KA, Tolonen TT, Bracken H, Stenman UH, Tammela TL, Saramäki OR, Visakorpi T. Association of SPINK1 expression and TMPRSS2:ERG fusion with prognosis in endocrine-treated prostate cancer. *Clin. Cancer Res.* 2010; 16:2845–2851. doi: 10.1158/1078-0432.CCR-09-2505 Medline. [PubMed: 20442300]
14. Davis ME, Zuckerman JE, Choi CH, Seligson D, Tolcher A, Alabi CA, Yen Y, Heidel JD, Ribas A. Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles. *Nature.* 2010; 464:1067–1070. doi:10.1038/nature08956 Medline. [PubMed: 20305636]
15. Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, Wongvipat J, Smith-Jones PM, Yoo D, Kwon A, Wasielewska T, Welsbie D, Chen CD, Higano CS, Beer TM, Hung DT, Scher HI, Jung ME, Sawyers CL. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science.* 2009; 324:787–790. doi:10.1126/science.1168175 Medline. [PubMed: 19359544]
16. Ozaki N, Ohmuraya M, Hirota M, Ida S, Wang J, Takamori H, Higashiyama S, Baba H, Yamamura K. Serine protease inhibitor Kazal type 1 promotes proliferation of pancreatic cancer cells through the epidermal growth factor receptor. *Mol. Cancer Res.* 2009; 7:1572–1581. doi: 10.1158/1541-7786.MCR-08-0567 Medline. [PubMed: 19737965]
17. Di Lorenzo G, Tortora G, D'Armiento FP, De Rosa G, Staibano S, Autorino R, D'Armiento M, De Laurentiis M, De Placido S, Catalano G, Bianco AR, Ciardiello F. Expression of epidermal growth factor receptor correlates with disease relapse and progression to androgen-independence in human prostate cancer. *Clin. Cancer Res.* 2002; 8:3438–3444. Medline. [PubMed: 12429632]
18. Schlomm T, Kirstein P, Iwers L, Daniel B, Steuber T, Walz J, Chun FH, Haese A, Kollermann J, Graefen M, Huland H, Sauter G, Simon R, Erbersdobler A. Clinical significance of epidermal growth factor receptor protein overexpression and gene copy number gains in prostate cancer. *Clin. Cancer Res.* 2007; 13:6579–6584. doi:10.1158/1078-0432.CCR-07-1257 Medline. [PubMed: 18006757]
19. Fukuoka S, Fushiki T, Kitagawa Y, Sugimoto E, Iwai K. Competition of a growth stimulating-/cholecystokinin (CCK) releasing-peptide (monitor peptide) with epidermal growth factor for binding to 3T3 fibroblasts. *Biochem. Biophys. Res. Commun.* 1987; 145:646–650. doi: 10.1016/0006-291X(87)91013-8 Medline. [PubMed: 3496093]
20. Slovin SF, Kelly WK, Wilton A, Kattan M, Myskowski P, Mendelsohn J, Scher HI. Anti-epidermal growth factor receptor monoclonal antibody cetuximab plus Doxorubicin in the treatment of metastatic castration-resistant prostate cancer. *Clin. Genitourin. Cancer.* 2009; 7:E77–E82. doi:10.3816/CGC.2009.n.028 Medline. [PubMed: 19815486]
21. Kinkade CW, Castillo-Martin M, Puzio-Kuter A, Yan J, Foster TH, Gao H, Sun Y, Ouyang X, Gerald WL, Cordon-Cardo C, Abate-Shen C. Targeting AKT/mTOR and ERK MAPK signaling inhibits hormone-refractory prostate cancer in a preclinical mouse model. *J. Clin. Invest.* 2008; 118:3051–3064. Medline. [PubMed: 18725989]
22. Zhang B, Strauss AC, Chu S, Li M, Ho Y, Shiang KD, Snyder DS, Huettner CS, Shultz L, Holyoake T, Bhatia R. Effective targeting of quiescent chronic myelogenous leukemia stem cells by histone deacetylase inhibitors in combination with imatinib mesylate. *Cancer Cell.* 2010; 17:427–442. doi:10.1016/j.ccr.2010.03.011 Medline. [PubMed: 20478526]
23. Goldstein AS, Huang J, Guo C, Garraway IP, Witte ON. Identification of a cell of origin for human prostate cancer. *Science.* 2010; 329:568–571. doi:10.1126/science.1189992 Medline. [PubMed: 20671189]
24. Small EJ, Fontana J, Tannir N, DiPaola RS, Wilding G, Rubin M, Iacona RB, Kabbavar FF. A phase II trial of gefitinib in patients with nonmetastatic hormone-refractory prostate cancer. *BJU Int.* 2007; 100:765–769. doi:10.1111/j.1464-410X.2007.07121.x Medline. [PubMed: 17822457]
25. Curigliano G, Pelosi G, De Pas T, Renne G, De Cobelli O, Manzotti M, Spitaleri G, de Braud F. Absence of epidermal growth factor receptor gene mutations in patients with hormone refractory prostate cancer not responding to gefitinib. *Prostate.* 2007; 67:603–604. doi:10.1002/pros.20530 Medline. [PubMed: 17290443]
26. Canil CM, Moore MJ, Winquist E, Baetz T, Pollak M, Chi KN, Berry S, Ernst DS, Douglas L, Brundage M, Fisher B, McKenna A, Seymour L. Randomized phase II study of two doses of gefitinib in hormone-refractory prostate cancer: a trial of the National Cancer Institute of Canada-

- Clinical Trials Group. *J. Clin. Oncol.* 2005; 23:455–460. doi:10.1200/JCO.2005.02.129 Medline. [PubMed: 15659491]
27. Sridhar SS, Hotte SJ, Chin JL, Hudes GR, Gregg R, Trachtenberg J, Wang L, Tran-Thanh D, Pham NA, Tsao MS, Hedley D, Dancey JE, Moore MJ. A multicenter phase II clinical trial of lapatinib (GW572016) in hormonally untreated advanced prostate cancer. *Am. J. Clin. Oncol.* 2010; 33:609–613. doi:10.1097/COC.0b013e3181beac33 Medline. [PubMed: 20042973]

Fig. 1. Targeted therapies

(A) SPINK1 secreted from prostate cancer cells can stimulate EGFR dimerization, phosphorylation and downstream signaling through phosphoinositide-3-kinase (PI3K)/AKT, mitogen activated protein kinase (MAPK), or janus kinase (JAK) pathways in an autocrine loop. (B) In addition to small-molecule agents that block AR, PI3K/AKT, MAPK, or JAK signaling pathways, monoclonal antibodies against EGFR or SPINK1 could inhibit signal transduction by blocking the physical interaction between EGFR and the SPINK1 ligand. Antibody inhibition of EGFR-SPINK1 binding would cause receptor endocytosis and EGFR down-regulation, subsequently breaking the autocrine loop. Antibodies targeting EGFR would specifically block receptor dimerization, autophosphorylation, and downstream signaling. The effects of SPINK1 cannot be completely reversed by inhibition of EGFR, suggesting that SPINK1 may act as a ligand for other receptors or promote aggressive properties through other mechanisms.