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COMMENTARY

Ras-ling with new therapeutic targets for metastasis

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ABSTRACT

Successful cancer metastasis relies on the ability of cancer cells to survive independently of attachment to the extracellular matrix (ECM) and to overcome ECM-detachment-induced death programs. This can be accomplished through activating mutations in cellular oncogenes that subsequently lead to the inhibition of anoikis and to alterations in productive metabolism. One example of such an oncogene is Ras which is found to be mutated and hyperactivated in a variety of distinct cancers. Despite numerous studies on Ras, the precise molecular mechanisms that facilitate survival during ECM-detachment remain poorly understood. Recently, we discovered that ECM-detached cells harboring oncogenic Ras mutations require signaling through the PI(3)K/SGK1 signaling axis to promote survival. Furthermore, we found that oncogenic Ras can concurrently diminish PHLPP1 phosphatase levels, which results in a decrease in p38 MAPK-mediated activation of anoikis. Thus, our data suggest that cancer cells with activating Ras mutations can survive during ECM-detachment using downstream effector molecules that modulate distinct pathways. Overall, these data suggest that new therapeutic interventions that aim to mitigate SGK1 signaling and activate the p38 MAPK activity may aid in specifically targeting and eliminating metastatic cancer cells.

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Anoikis and metabolic alterations during ECM-detachment: 2 barriers to the survival of cancer cells

A significant number of disparate cell types require integrin-mediated attachment to the extracellular matrix (ECM) to ward off the induction of detachment-induced cell death programs.[1,2] In direct contrast, cancer cells acquire the capability to forego this requirement and thus can robustly survive during detachment from the ECM. This capacity for survival during ECM-detachment is acutely critical during the metastatic cascade, where cancer cells will be exposed to numerous periods of ECM-detachment and abnormal ECM environments during the dissemination of cancer cells throughout the body. Thus, it can be argued that ECM-detached cancer cells must evade detachment-induced cell death mechanisms at every step of the metastatic cascade; from localized invasion, to survival in the circulation, to colonizing a secondary site. Perhaps the most well-described cell death pathway that cancer cells evade during ECM-detachment is anoikis, which is defined as caspase-dependent apoptosis that is induced by loss of integrin-mediated attachment to ECM.[3] Much of our current understanding of anoikis has been accrued from a 3-dimensional cell culture model of mammary acini where a hollow lumen is generated (in part) by anoikis of centrally located cells.[4-6] Using this model, it has become abundantly clear that inhibition of anoikis is not sufficient to promote survival of ECM-detached cells in the luminal space. More specifically, ECM-detached mammary epithelial cells develop metabolic alterations that lead to diminished viability during ECM-detachment and resolving these metabolic deficiencies leads to the survival of ECM-detached cells in the luminal space[7,8]

A novel mechanism downstream of oncogenic ras that facilitates survival of ECM-detached cells

Strategies used by cancer cells to overcome metabolic deficiencies and evade anoikis have been revealed to be multi-faceted and diverse.[2,9-11] However, downstream signaling emanating from activated oncogenes is now appreciated to function to antagonize the induction of anoikis and to promote energy production. This phenomenon was first observed with ErbB2,[8] which is over-expressed in ~30% of breast cancers and can activate a variety of distinct downstream signaling pathways. We sought to expand on these studies by examining whether

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distinct oncogenic mutations would converge on specific downstream effector pathways to promote survival during ECM-detachment.[12,13] Given that hyperactivating mutations in the small GTPase Ras (via mutations in codon 12, 13, or 61), occur in approximately 30% of all cancers (most commonly in pancreatic (90%), colon (50%), and lung (30%), we sought to investigate the molecular mechanisms underlying the ability of oncogenic Ras to facilitate both anoikis evasion and productive metabolism during ECM-detachment.[14,15] In addition, these oncogenic mutations in Ras can plays a critical role promoting tumor progression, metastasis, and cell survival.[16,17]

As expected, we discovered that the overexpression of oncogenic Ras is sufficient to drive ATP generation during ECM-detachment while simultaneously blocking anoikis. However, when investigating the molecular mechanisms responsible for promoting ATP generation, we found that while phosphatidylinositol 3-kinase (PI(3)K) signaling was critically important, ATP generation did not require downstream signaling through AKT1.[12] Instead, we determined that the activity of serum and glucocorticoid-regulated kinase-1 (SGK1), a serine/threonine kinase known to function downstream of PI(3)K, is critical for ATP generation during ECM-detachment. SGK1 shares approximately 50% similarity with AKT1 in the catalytic domain. It is activated by mTORC2-dependent phosphorylation in the hydrophobic motif (S422) and phosphorylation of the activation loop (T256) by PDK1.[18,19] While SGK1 has been previously linked to glucose metabolism,[20,21] the pathology of certain metabolic syndromes,[22] and regulation of small GTPases,[23] multiple recent studies suggest an emerging role for SGK1 in tumorigenesis.[24] More specifically, several reports have observed elevated expression/activation of SGK1 in malignant tumors,[25-30] and thus our findings that SGK1 functions downstream of PI(3)K to promote ATP generation during ECM-detachment provide a possible mechanism by which SGK1 can contribute to cancer pathogenesis.

In subsequent examination of the importance of SGK1 kinase signaling on the survival of ECM-detached cells, we found that SGK1 activation promotes cell viability during ECM-detachment owing to its capacity to promote glucose uptake and ATP generation.[12] In support of this conclusion, expression of a constitutively active SGK1 (S422D) promotes luminal filling in a 3-dimensional cell culture model of mammary morphogenesis. Given these data, we next investigated the impact of SGK1-mediated ATP generation in enabling the survival of ECM-detached cancer cells that harbor mutations in oncogenic Ras. Indeed, inhibition of SGK1 signaling (via both pharmacological and shRNA based approaches) in HCT116 cells (a colon cancer cell line that contains an oncogenic mutation in K-Ras) substantially compromises metabolic activity and survival during ECM-detachment. Furthermore, we found that loss of SGK1 signaling significantly hinders anchorage independent growth, a classic hallmark of tumorigenic capacity. In aggregate, these data suggest that cancer cells that contain oncogenic Ras mutations can utilize PI(3)K/SGK1 signaling to rectify ECM-detachment-induced metabolic deficiencies in a fashion that promotes cell survival. In agreement with this inference, we observed a positive correlation between protein levels of oncogenic K-Ras levels and SGK1 kinase activity in colon cancer patients.[12] Thus, our findings suggest that SGK1 could be a potential therapeutic target to specifically compromise anchorage-independent growth in cancer cells containing oncogenic Ras mutations. In line with this possibility, other studies have already demonstrated that SGK1 activity is sufficient to overcome cell death mediated by PI(3)K and AKT1 inhibitors.[25,3,32] These findings suggest that tumor cells that acquire resistance to these inhibitors may do so through constitutive SGK1 activation. Furthermore, SGK1 inhibitors have begun to show promise in blocking cancer cell proliferation[33] and in potentiating the effects of radiotherapy.[34,35]

In addition to Ras-mediated promotion of ATP generation during ECM-detachment, hyperactivating mutations in Ras profoundly inhibit anoikis in a fashion that is independent of the SGK1-mediated effects on glucose metabolism. Given this, we were interested in discerning the effectors that operate downstream of Ras to potentiate anoikis evasion.[12] Interestingly, we found that ECM-detached cells expressing oncogenic Ras maintain phosphorylation of AKT1 (at S473) in the presence of robust inhibition of PI(3)K. These data suggest that Ras activation may antagonize phosphatase activity toward AKT1 and thus facilitate evasion of anoikis. AKT1 is known to be dephosphorylated at S473 by the phosphatase PHLPP1 (PH Domain Leucine Rich Repeat Protein Phosphatase 1),[36,37] which has been shown to function as a tumor suppressor.[38-41] In support of the possibility that Ras-mediated inhibition of AKT1 dephosphorylation blocks anoikis, we found that expression of oncogenic Ras results in a significant loss of PHLPP1 protein. Furthermore, shRNA-mediated reduction of PHLPP1 inhibits anoikis and can promote the survival of ECM-detached cells in the luminal space of mammary acini. Additionally, re-introduction of PHLPP1 into cells harboring oncogenic Ras mutations sensitizes ECM-detached cells to anoikis and hinders anchorage independent growth.

Interestingly, in the aforementioned experiments, we did not detect alterations in the phosphorylation of

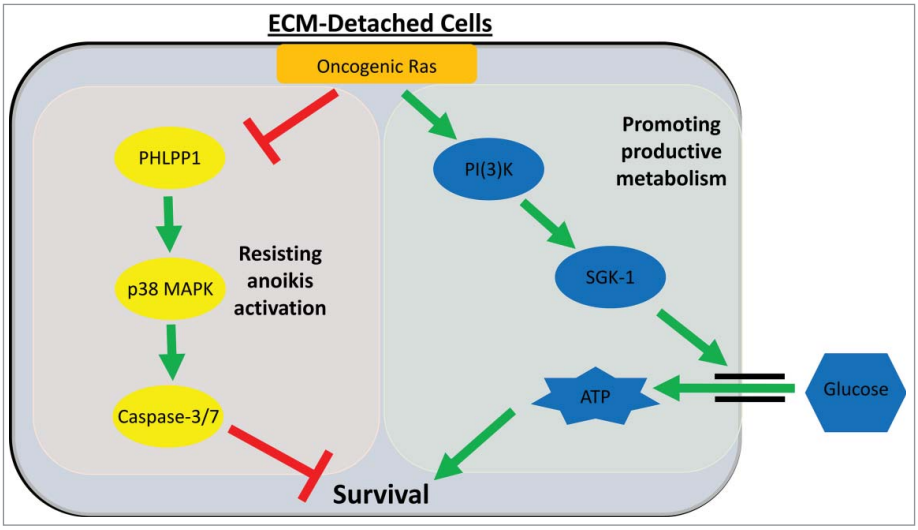

Figure 1. Oncogenic Ras promotes productive metabolism and blocks anoikis via divergent downstream effectors. During ECM-detachment, cells harboring oncogenic Ras mutations signal via a PI(3)K/SGK1-mediated pathway to increase glucose uptake, ATP generation, and survival (right, green box). Simultaneously, oncogenic Ras diminishes PHLPP1 levels to overcome p38 MAPK-mediated anoikis activation (left, red box).

AKT1 (at S473) when PHLPP1 was reintroduced into cancer cells with Ras mutations. This appears to be due to Ras-mediated downregulation of the scaffold protein FKBP5, which is required to target PHLPP1 to S473 on AKT1.[42] Thus, our findings suggest that PHLPP1-mediated induction of sensitivity to anoikis involves a pathway distinct from AKT1. Indeed, we found that PHLPP1-mediated induction of anoikis is a direct result of downstream activation of the p38 MAPK pathway. This stimulation of p38 MAPK by PHLPP1 is conceivably due to PHLPP1-mediated dephosphorylation of MST1, which increases MST1 kinase activity.[43] MST1 activity has been previously shown to function upstream of kinases that can activate p38 MAPK. However, the precise mechanism by which PHLPP1 activity leads to p38 MAPK and anoikis has yet to be fully delineated. That being said, we did observe a negative correlation between oncogenic K-Ras levels and p38 MAPK activation in colon cancer patients,[12] suggesting that inhibition of p38 MAPK due to Ras-mediated downregulation of PHLPP1 may be operative in patient populations.

Conclusions and perspectives

Given that cancer metastasis accounts for approximately 90% of cancer related deaths,[44] there is an ardent need to develop novel therapeutic strategies aimed at specifically eliminating metastatic cancer cells. Additionally, one of the most commonly activated proteins across a diversity of distinct cancers is Ras, yet targeted therapeutics against Ras mutant cells are limited or poorly effective.[17] In our recent study (summarized in Fig. 1),[12] we have found that SGK1 is critically important downstream of Ras/PI(3)K activation to promote ATP generation and cancer cell survival during ECM-detachment. At the same time, oncogenic Ras suppresses PHLPP1 to overcome p38 MAPK-mediated anoikis induction. These data unveil new targets for therapeutic intervention in cancer cells with activating Ras mutations. More specifically, our data suggest that simultaneous inhibition of SGK1 activity and activation of p38 MAPK signaling, could be an efficacious therapeutic strategy for patients whose cancers are driven by oncogenic Ras mutations. Furthermore, since the SGK1 and p38 MAPK-mediated effects of Ras are uniquely important in ECM-detached cells, such a regimen may be particularly helpful in antagonizing tumor progression and metastasis. Additional preclinical studies aimed at assessing the efficacy of this potential strategy will be important to the ultimate translation of these findings into meaningful clinical outcomes.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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