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INVITED COMMENTARY ON HOT ARTICLES

Cancer is the second leading cause of death in the world (18%), after heart disease (21%). Among about 18 million new cases of cancers diagnosed each year, about one third is skin cancer. However, 95% of skin cancer is either basal cell carcinoma or squamous cell carcinoma, which has a mortality of less than 0.5%. The majority of cancer-related deaths are actually caused by malignancies derived from the digestive system, including esophagus, stomach, small intestine, colon, rectum, anus, liver, gallbladder and pancreas[1]. The main feature that makes these cancers deadly is metastasis, a process that cancer cells break off from their original location and invade other parts of the organ. The majority of skin cancers do not have this capacity; therefore, they can be easily treated before becoming life threatening. Esophageal cancer, on the other hand, is highly metastatic. Therefore, understanding the molecular mechanisms behind its metastasis is of great values for developing better treatment strategies. A study by Chen et al[2] published in the World J Gastroenterol 18(9): 915-922, 2012 examined the role of S100A4, one of the well-known cancer metastatic markers, in esophageal squamous cell carcinoma (ESCC) in vitro and in vivo, in animal models as well as in clinical human specimens, and clearly demonstrated a reliance of the invasiveness of esophageal cancer on this small calcium-binding protein[2].

A little biography of S100A4: Short but hot
S100A4 was discovered in the mid 1980s by several laboratories independently. One of these laboratories be-
longed to Daniel Nathans, MD (10/30/1928-11/16/1999) (Figure 1), the Nobel Prize winner in Physiology/Medicine 1978 for his landmark discovery of restriction enzymes. In 1983, one of his post-doctoral fellows, Daniel I Linzer, PhD, was constructing a cDNA library from serum-stimulated mouse 3T3 fibroblasts and found that a clone named 18A2 was highly up-regulated by serum exposure. There seemed to be many laboratories in the late 70s and early 80s of the 20th century which were interested in the effect of serum on gene expression. That was also how and when serum response factor (SRF) was discovered. In the following year, Linzer took a job at Northwestern University in Illinois (now he is the Provost of this school) and continued his study on 18A2. He determined that 18A2 coded for a calcium binding protein of 101 amino acids, much similar to the members of S100 family, a group of small peptides that are known to be 100% soluble in saturated ammonia sulfate. He also compared the sequence of 18A2 with 2A9, a human clone that was published a year earlier, and found a 57% nucleotide and 62% amino acid homology between them. It might be due to the difference of species origin, Linzer was pretty sure that these two sequences represented different genes. Around that time and shortly thereafter, several other laboratories also published similar sequences and each of which was given a different name, including p9Ka from rat mammary cells, 42A from rat neuronal cells, pEL98 from mouse fibroblasts, CAPL from Aplysia neurons, mts1 from metastatic tumor cells, and FSP1 from mouse fibroblasts. Despite the individuality of each of these studies, there were some common features shared among their discoveries: (1) serum inducibility; (2) around 100 amino acids; and (3) similarity to S100 calcium binding proteins. Although all of these sequences eventually turned out to be for a single molecule - S100A4, each of these studies made unique contributions to our knowledge today about S100A4. The last two studies warrant an extra attention, because one established the connection between S100A4 and cancer metastasis and the other associated it to fibroblast phenotype. Now we know that S100A4 is a prognostic marker for metastatic cancers as well as a marker for epithelial-mesenchymal transition. However, both of these studies went a little bit too far by calling this molecule metastatic-

### Functions of S100A4: Motivation to move

Up to date, S100 family includes 25 members with common characteristics such as low molecular weight, two calcium binding sites of the helix-loop-helix (“EF-hand type”) conformation, and complete solubility in ammonium sulfate at pH 7. They have been implicated in regulation of protein phosphorylation, transcription factor activation, calcium homeostasis, cytoskeleton reorganization, cell migration, cell growth and death.

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S100A4 is naturally expressed in various cell types including both cancer and normal cells, and its elevation is usually associated with cell motility. It appears that whenever cell migration is required, such as wound healing, angiogenesis and cancer metastasis, S100A4 is activated. Like other members of S100 family, S100A4 works like a calcium sensor. Upon calcium binding, S100A4 goes through a series of conformational changes, which allow the molecule to interact with its targets, such as nonmuscle myosin heavy chain (MHC II A) and liprin β1, to facilitate cell migration and cancer metastasis. However, both of these studies went a little bit too far by calling this molecule metastatic-transitional. Nonetheless, its association with transcription factors like p53 might explain some of its roles in the nucleus. It has been postulated that S100A4 binding to the tetramerization domain of p53 favors p53 oligomerization and thereby facilitates p53 nuclear translocation. On the other hand, extracellular S100A4 has been demonstrated to stimulate MMP-13 expression in chondrocytes in a receptor for advanced glycation end products (RAGE)-dependent manner, while its inductivity on neuron growth was found to be RAGE irrelevant. More complicatedly, S100A4 has been found in association with cell death in a conflict way, it inhibits apoptosis in pancreatic cancer but promotes it in osteosarcoma cells.

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### S100A4 in cancers: A facilitator, not a generator

Elevation of S100A4 has been found in almost every metastatic cancer known, including breast, prostate, urinary bladder, lung, esophageal, gastric, colon, pancreatic, liver, gallbladder and
thyroid carcinomas\textsuperscript{[39]}. More direct evidence for the essential role of S100A4 in cancer metastasis perhaps comes from \textit{in vitro} studies and animal models, which have shown that overexpression of S100A4 in non-metastatic tumor cells confers a metastatic phenotype, just as demonstrated in the study by Chen et al\textsuperscript{[2]} as well as several others\textsuperscript{[17,42,43]}; whereas, knockdown of S100A4 in metastatic tumor cells curtails their invasive capability\textsuperscript{2,42,43].}

It should be pointed out though that S100A4 is not an oncogene product. As shown by transgenic studies\textsuperscript{[18,44]}, mice carrying extra copies of \textit{S100A4} gene develop normally as wild-type and have no increased risk of cancer. However, when these mice mated with cancer mice, their offspring showed increased number of tumors distant from their primary location\textsuperscript{[44]}. Therefore, S100A4 is not a cancer generator but a metastatic facilitator.

S100A4 has been studied extensively in other cancers, especially in breast cancer. In esophageal cancer, there are about a dozen of publications so far, mostly focusing on squamous cell carcinoma. The earliest study that can be found was done by a Japanese group\textsuperscript{[33]}, showing an elevated expression of \textit{S100A4} protein in surgically resected ESCC, and a possible association with esophageal cancer progression. However, a later study reported an opposite result, showing that 11 out of 16 S100 family members examined, including \textit{S100A4}, were down-regulated at transcriptional level in tumors compared with adjacent normal tissues\textsuperscript{[36]}. In 2010, a Chinese research team used RNA interference technology to knock down S100A4 in metastatic esophageal tumor cells and grafted them in nude mice\textsuperscript{[46]}. They noticed that tumor growth was significantly inhibited by S100A4 deficiency, and E-cadherin expression was reciprocal to the level of S100A4. Unfortunately, the study had little impact because it was published in a local journal in Chinese. However, the idea of xenografting has recently advanced to a new cancer treatment strategy - the “avatar” mice. Principally, it is to take tumor tissue from a patient and graft it in nude mice to create a personalized colony of mice carrying exact that patient’s cancer, and then test every potential treatment combinations in mice before selecting the best one to treat that patient. Manuel Hidalgo, the Director of the Spanish National Cancer Research Center in Madrid, has been practicing this approach for pancreatic cancer patients over years and showed a clear advantage in drug responses\textsuperscript{[46,61]}, and now more and more researchers believe that this idea holds a great promise in cancer treatment in the future.

In the study by Chen et al\textsuperscript{[2]}, the research team cleverly used two ESCC cell lines, EC109 (highly invasive) and TE13 (non-invasive), and successfully made these cells switch characters by down-regulation of S100A4 in EC109 and up-regulation of S100A4 in TE13. They provided \textit{in vitro} and \textit{in vivo} evidence that the level of S100A4 determines the metastatic status of the cancer.

There are two main subtypes of esophageal cancer: ESCC and esophageal adenocarcinoma (EAC). Although nearly 95% of esophageal cancer is ESCC, EAC has been rising by 6-fold annually in Americans and now its increase rate exceeds the rate for any other type of cancers. Overexpression of S100A4 was also reported in EAC and its correlation with lymph node metastasis was found significant\textsuperscript{[40,41]}

Although the exact molecular mechanisms how S100A4 promotes cancer metastasis still need to be further examined, based on various studies, one possible explanation could be that S100A4 binding to liprin \beta1 inhibits its phosphorylation\textsuperscript{[47]}, and thereby prevents its interaction with liprin \alpha1. As a result, liprin \alpha1 fails to recruit leukocyte common antigen-related (LAR) protein\textsuperscript{[51]}, a phosphatase, to focal adhesions. Without LAR to dephosphorylate \beta-catenin\textsuperscript{[52]}, \beta-catenin becomes activated to leave E-cadherin and results in the collapse of adherens junctions, allowing cells to migrate. As found in our study, the dissociation of \beta-catenin from E-cadherin causes E-cadherin ubiquitination and degradation\textsuperscript{[53]}, which might at least in part explains why S100A4 elevation is often found in association of E-cadherin loss, as shown in the study by Chen et al\textsuperscript{[2]}.

\textbf{S100A4 in normal situation: An innocent bystander}

As discussed above, S100A4 is expressed wherever cell migration is required, regardless normal or pathological situation. However, most of S100A4 studies focus on its bad side, such as cancer metastasis and organ fibrosis. Its good side has been continually overlooked. If we go back to the story that S100A4 was discovered in an experiment of serum stimulated fibroblasts, we know that S100A4 is innocent. Cells, including fibroblasts, in our body normally do not come into a direct contact with serum unless there is an injury. Therefore, when cells are suddenly exposed to serum, as the experiment done in Nathans’ lab, they naturally interpret it as a signal of a wound. Therefore, a transcriptional program for wound healing gets activated immediately to battle against injury: S100A4 is just one of the players in this battle. So is SRF, and so are many SRF-regulated genes (e.g., C-FOS, EGR-1, CCN1, CTGF, FGF10, etc)\textsuperscript{[39]}. All these genes contain a common regulatory element \textit{C\textsuperscript{A}rG} box, which SRF recognizes to bind. \textit{S100A4} gene also contains such element in its promoter region\textsuperscript{[53]}, suggesting a possible regulation by SRF. \textit{In vivo}, S100A4 activation has been found in various wound healings, and its contributions to tissue repair and modification are indisputable\textsuperscript{[16,56]}.

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