

- [ScienceWatch Home](#)
- [Inside This Month...](#)
- [Interviews](#)

- [Featured Interviews](#)
- [Author Commentaries](#)
- [Institutional Interviews](#)
- [Journal Interviews](#)
- [Podcasts](#)

Analyses

- [Featured Analyses](#)
- [What's Hot In...](#)
- [Special Topics](#)

Data & Rankings

- [Sci-Bytes](#)
- [Fast Breaking Papers](#)
- [New Hot Papers](#)
- [Emerging Research Fronts](#)
- [Fast Moving Fronts](#)
- [Corporate Research Fronts](#)
- [Research Front Maps](#)
- [Current Classics](#)
- [Top Topics](#)
- [Rising Stars](#)
- [New Entrants](#)
- [Country Profiles](#)

About Science Watch

- [Methodology](#)
- [Archives](#)
- [Contact Us](#)
- [RSS Feeds](#)



- [Interviews](#)
- [Analyses](#)
- [Data & Rankings](#)

2009 : September 2009 - New Hot Papers : Sendurai Mani & Robert Weinberg on Linking EMT and CSC During Cancer Progression

NEW HOT PAPERS - 2009

September 2009



Sendurai A. Mani and Robert A. Weinberg talk with ScienceWatch.com and answer a few questions about this month's New Hot Paper in the field of Molecular Biology & Genetics.



Article Title: The epithelial-mesenchymal transition generates cells with properties of stem cells

Authors: Mani, SA;Guo, W;Liao, MJ;Eaton, EN;Ayyanan, A;Zhou, AY; Brooks, M;Reinhard, F;Zhang, CC;Shipitsin, M;Campbell, LL;Polyak, K; Briskin, C;Yang, J;Weinberg, RA

Journal: CELL, Volume: 133, Issue: 4, Page: 704-715, Year: MAY 16 2008

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SW: Why do you think your paper is highly cited?

Currently, a number of groups are investigating the biology of tumor initiation, invasion, and metastasis, as well as chemoresistance. Several key factors that regulate these processes have been identified. The aberrant activation of epithelial-to-mesenchymal transition (EMT) has been linked with many of these processes during tumor progression.

In addition, recent findings have demonstrated that cancer stem cells also play an important role in many of the above processes. Strikingly, we found that epithelial cells that have undergone EMT not only appear mesenchymal but also behave like stem cells. This finding completed a loop—EMT plays a key role during cancer progression by generating cancer **stem cells**—and touched upon many different areas.

This work initiated a new set of questions that are currently being answered by many new publications. In addition, our finding also demonstrated that normal stem-like cells can be generated via EMT, which links this finding to research related to normal cellular processes and embryo development.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

Our finding reports a new discovery. For the first time, our paper linked two highly studied and seemingly important processes during cancer progression—EMT and cancer stem cells (CSC). Previously, these ideas were believed to be completely independent processes.

Our study showed that CSC is a state that can be generated from more differentiate tumor cells instead of solely via the transformation of local stem cells. Our finding also describes a new methodology. Specifically, that one can generate large numbers of stem-like cells

from differentiated epithelial cells simply by inducing transient EMT.

SW: Would you summarize the significance of your paper in layman's terms?

Our body consists of two major types of cells, epithelial and mesenchymal. The epithelial cells are tightly attached with one another and are less migratory than mesenchymal cells, due to the continued presence of cell-cell adhesion molecules. On the other hand, the mesenchymal cells are loosely bound and are highly migratory.

In humans, more than 80% of all tumors originate in epithelial cells and initially develop into benign tumors due to the continued expression of the cell-cell adhesion molecules. In order to break away from these bonds and become invasive and metastatic, epithelial cancer cells activate a normally latent embryonic program known as EMT.

Recent findings have demonstrated that epithelial tumors (carcinomas) contain multiple types of cancer cells, including both differentiated cancer cells and cancer stem cells. CSCs can initiate the formation of tumors with high efficiency as well as support the growth of the tumor mass. These CSCs are also proposed to play an important role in metastatic seeding and therapy resistance.

Previously, cells that have undergone EMT and CSCs were believed to independently contribute to the diversity of different cell types within tumors. However, we discovered that, through EMT, differentiated tumors can generate CSCs.

These findings suggest that EMT may act as a central regulator of cancer metastasis by not only enabling cancer cells to disseminate but also by enabling the initiation of tumor growth in the new location. It also suggests that activation of EMT may help to sustain primary tumor growth.

In addition, CSCs are resistant to numerous conventional therapies. Therefore, the molecular mechanisms that regulate EMT could serve as novel therapeutic targets for preventing tumor recurrence and treating resistant tumors.

SW: How did you become involved in this research and were there any problems along the way?

Bob Weinberg has created an excellent work environment where new discoveries are extremely possible. He recruits people with different expertise. He runs the lab like a Chairman of the Department, and his lab members are like individual faculty members. He allows each researcher time to develop their own idea, and he plays a key role in shaping their findings into something novel.

He makes sure that researchers in his laboratory address key problems in cancer biology, and that they meet other scientists in the field on a regular basis. For example, Bob organizes weekly meetings with several other MIT biologists, including Dr. Philip Sharp, Dr. Tyler Jacks, Dr. Rudolph Jaenish, Dr. Frank Solomon, Dr. Jackie Lee, and several others.

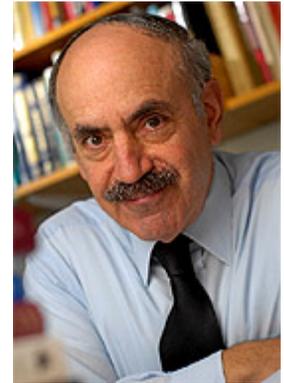
At one of the meetings, someone from the Jaenish laboratory mentioned that he could reprogram adult cells by modulating expression of genes in adult cells. I immediately thought about the EMT process and felt there may be some similarity whereby the EMT process may reprogram the adult epithelial cell as well.

I went back to the lab and approached another postdoc, Dr. Mai-Jing Liao, to help me to analyze some of my samples, which were induced to undergo EMT. Mai-Jing did not believe that this was possible; however, he agreed to help. To our surprise, we found that the cells that had undergone EMT displayed stem cell properties.

SW: Where do you see your research leading in the future?

Since EMT plays a very central role in promoting the spread of breast cancer and the development of therapeutic resistance by cancer cells, tools to identify the cells that have undergone EMT, and thus exhibit stem cell properties, will improve our ability to predict the future spread of epithelial cancer.

This ability to identify patients whose cancer is likely to spread or relapse will enable doctors to treat these patients accordingly, thereby preventing the spread of the cancer. This finding should also lead to development of new therapeutic options for eliminating these highly aggressive cancer stem cells with



*Coauthor
Robert A. Weinberg*

the multiple traits necessary for metastasis.

Our finding showed that large populations of CSCs or normal stem cells can also be generated from differentiated normal/cancer cells, and this should facilitate the study of CSC biology because large populations of CSC were previously very difficult to obtain. For example, sufficient CSC can now be obtained for the preclinical discovery necessary for the development of compounds to selectively inhibit the growth of the drug-resistant CSC populations.

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KEYWORDS: BREAST-CANCER CELLS; TRANSCRIPTION FACTOR SNAIL; TUMOR PROGRESSION; E-CADHERIN; MAMMARY-GLAND; METASTASIS; EXPRESSION; TWIST; IDENTIFICATION; TRANSFORMATION.

Robert A. Weinberg related information:

[Podcast](#) (July 2009).

[Interview](#) (*Science Watch*® Newsletter Classic Interview, August 1992).

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[back to top](#) 

2009 : [September 2009 - New Hot Papers](#) : Sendurai Mani & Robert Weinberg on Linking EMT and CSC During Cancer Progression

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