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Must Read  
 F1000 Factor **6.6**  
 EndNote

**Rac1b and reactive oxygen species mediate MMP-3-induced EMT and genomic instability.**

Radisky DC, Levy DD, Littlepage LE, Liu H, Nelson CM, Fata JE, Leake D, Godden EL, Albertson DG, Nieto MA, Werb Z, Bissell MJ

*Nature* 2005 Jul 7 **436**(7047):123-7 [[abstract on PubMed](#)] [[citations on Google Scholar](#)] [[related articles](#)] [[full text](#)]

**Selected by** | Kenneth Yamada / Alex Toker / Jonathan Chernoff  
 First evaluation 14 Jul 2005 | Latest evaluation 21 Jul 2005  
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**Faculty Comments**

**Faculty Member**

**Kenneth Yamada**  
 National Institutes of Health (NIH), United States of America  
 CELL BIOLOGY

- Hypothesis
- New Finding

**Comments**

**This paper provides the first identification of a pathway by which excess protease activity can transform normal cells to malignant.** The authors find that MMP-3 (stromelysin-1) induces Rac1b, which in turn stimulates reactive oxygen species. The latter produce DNA damage and genomic instability, and also induce the transcription factor Snail to produce an epithelial-mesenchymal transition, thereby promoting the formation of tumors.

**Competing interests:** None declared  
 Evaluated 14 Jul 2005

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**Alex Toker**

Beth Israel Deaconess Medical Center, United States of America  
 CELL BIOLOGY

- Hypothesis
- New Finding

**This study reports on the mechanism by which the enzyme MMP3 (matrix metalloproteinase 3), also known as stromelysin-1, promotes genetic instability and EMT (epithelial to mesenchymal transition).** MMP3 is frequently up-regulated in many tumors and is also known to promote transformation and EMT in vitro. MMP3 is capable of degrading matrix molecules as well as cleaving precursor forms of various growth factors. However, up until now the precise mechanisms by which MMP3 modulates tumor progression by stimulating EMT and promoting genetic instability had remained elusive. This study shows that cells treated with MMP3 show alterations in the organization of the actin cytoskeleton, which in turn induces the expression of an alternatively spliced form of Rac1b. GTPases such as Rac1 are known to promote release of reactive oxygen species (ROS) and indeed release of ROS mediated by MMP3 leads to genetic instability, concomitant with induction of EMT, mediated by the transcription factor Snail.

**Competing interests:** None declared  
 Evaluated 18 Jul 2005

[How to cite this evaluation](#)

**Jonathan Chernoff**

Fox Chase Cancer Center,  
United States of America  
CELL BIOLOGY



**This article implicates a specific splice variant of the small GTPase Rac1 in metalloproteinase-3 (MMP3)-induced epithelial-mesenchymal transition (EMT) and genomic instability.** The splice variant in question, Rac1b, had previously been shown to be amplified in a variety of cancers, but its function remained obscure. Here, the authors show that this isoform of Rac1 is specifically induced by MMP3 and that it signals, via reactive oxygen species, to increase expression of the transcription factor Snail (which is associated with EMT) and to induce genomic instability. These findings help clarify the role of matrix-generated factors in inducing aberrant signaling in epithelial cells.

**Competing interests:** None declared  
Evaluated 21 Jul 2005

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## Faculty Comments

### How to cite the Faculty of 1000 Biology evaluation(s) for this paper

**1) To cite all the evaluations for this article:**

Faculty of 1000 Biology: evaluations for Radisky DC et al *Nature* 2005 Jul 7 436 (7047) :123-7  
<http://www.f1000biology.com/article/id/1026729/evaluation>

**2) To cite an evaluation by a specific Faculty member:**

Kenneth Yamada: Faculty of 1000 Biology, 14 Jul 2005 <http://www.f1000biology.com/article/id/1026729/evaluation>

Alex Toker: Faculty of 1000 Biology, 18 Jul 2005 <http://www.f1000biology.com/article/id/1026729/evaluation>

Jonathan Chernoff: Faculty of 1000 Biology, 21 Jul 2005 <http://www.f1000biology.com/article/id/1026729/evaluation>