

# This Week's Citation Classic®

Witkin E M. Ultraviolet mutagenesis and inducible DNA repair in *Escherichia coli*. *Bacteriol. Rev.* 40:869-907, 1976.

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This article was the first comprehensive review of emerging evidence for the "SOS hypothesis," which proposed that damage to DNA by many mutagens and carcinogens initiates a regulatory response in *Escherichia coli* resulting in the derepression of many genes and causing profound changes in cellular activities. [The SCI® indicates that this paper has been cited in over 1,265 publications.]

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One day in 1972, at Rutgers, I received an unpublished memorandum from Miroslav Radman, a young postdoctoral fellow at Harvard whom I had met when he was a graduate student in Brussels. Radman's reinterpretation of a 1953 observation by J. Weigle had led him to suggest that DNA damage in *Escherichia coli* induces a mutagenic mode of DNA replication, which he called "SOS replication" and to which he ascribed the repair and mutagenesis of heavily UV-irradiated bacteriophages that Weigle had shown required the UV irradiation of the bacterial host. He proposed that the same inducible repair activity causes bacterial UV mutagenesis, and that SOS replication is induced by the same regulatory signal (DNA damage) that activates latent bacterial viruses (prophages). I was excited by these ideas because they seemed to connect with and to link together two seemingly unrelated conclusions I had reached five years earlier, and I thought that perhaps Radman and I held different pieces of an important puzzle.

Since my first encounter with *E. coli* as a student in Cold Spring Harbor, I was intrigued by two distinct

effects of UV: filamentous growth (a cell-division defect seen in some strains) and UV-induced mutagenesis. By 1967, at SUNY Downstate Medical Center, I had concluded that filamentous growth is due to the induction by UV of a cell-division inhibitor by a process similar to induction of  $\lambda$  prophage in lysogenic strains.<sup>1</sup> I proposed that certain bacterial repressors may be inactivated by the same signal that destroys  $\lambda$  repressor, a signal initiated by DNA damage. In the same year, I also concluded that UV mutagenesis in *E. coli* is due to a process of error-prone DNA repair at sites of UV damage. Specifically, I proposed that UV-induced mutations were due to insertion of incorrect nucleotides opposite noncoding UV photoproducts in the template, a process now called translesion DNA replication.

Although I communicated my enthusiasm for his ideas to Radman, I was not convinced that bacterial UV mutagenesis was due to an inducible activity. Radman was discouraged by my doubts, and especially by the total lack of response to his memorandum by others to whom he had sent it.

At just this time in 1972, a group in Paris led by the late Jacqueline George published elegant studies<sup>2</sup> on a mutant (Tif<sup>-</sup>) that had earlier been shown to express both filamentous growth and  $\lambda$  prophage induction, without DNA damage, at high temperatures. Their work showed that the Weigle effect, too, was heat-inducible in Tif mutants. I was then able to use the Tif mutant (in which heat mimics UV) to demonstrate the inducibility of the activity responsible for bacterial UV mutagenesis.<sup>3</sup> Radman, elated, published the SOS hypothesis.<sup>4</sup> With a small group of converts, we then began an intensive and delightfully cooperative effort to identify and characterize additional DNA damage-inducible activities and to convince others of their reality and broad scope. Regulation of the SOS response is now well understood<sup>5</sup> and many of its components, including SOS mutagenesis,<sup>6</sup> are subjects of active investigation.

The high citation frequency of the 1976 review reflects the hidden gold still being mined in the bacterial SOS response, the increasing attention to DNA damage-inducible responses in higher organisms, and the recognition that some of these may contribute to carcinogenesis in human cells.

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3. Witkin E M. Thermal enhancement of ultraviolet mutability in a *tif-1* *uvrA* derivative of *Escherichia coli* B/r: evidence that ultraviolet mutagenesis depends upon an inducible function. *Proc. Nat. Acad. Sci. USA* 71:1930-4, 1974. (Cited 215 times.)
4. Radman M. Phenomenology of an inducible mutagenic DNA repair pathway in *Escherichia coli*: SOS repair hypothesis. (Prokash L, Sherman F, Miller M, Lawrence C & Tabor H W, eds.) *Molecular and environmental aspects of mutagenesis*. Springfield, IL: Thomas, 1974. p. 128-42.
5. Little J W & Mount D W. The SOS regulatory system of *Escherichia coli*. *Cell* 29:11-22, 1982.
6. Walker G C. Mutagenesis and inducible responses to deoxynucleic acid damage in *Escherichia coli*. *Microbiol. Rev.* 48:60-93, 1984.