

Double strand break repair triggers genome plasticity in *Streptomyces*

Grégory Hoff¹, Claire Bertrand¹, Emilie Piotrowski¹, Stephen McGovern², François Lecointe²,

Annabelle Thibessard¹ and Pierre Leblond^{1*}

¹INRA-Université de Lorraine, Dynamique des Génomes et Adaptation Microbienne, UMR 1128, Vandœuvre-lès-Nancy, F-54506, France (pierre.leblond@univ-lorraine.fr)

²Institut Micalis, INRA, AgroParisTech, Université Paris-Saclay, 78350 Jouy-en-Josas, France.

Double strand breaks (DSB) are the most detrimental damage that bacterial cells have to cope with. Two main DSB repair pathways, namely homologous recombination (HR) and non-homologous end joining (NHEJ) are in charge of DSB repair. HR relies on an intact copy of the damaged DNA molecule as a template. On the other hand, NHEJ, which is presumably present in only 20% to 25% of the bacteria, is considered as a mutagenic pathway. Hence, in the absence of template, NHEJ is an error-prone mechanism triggering nucleotide additions or deletions at DSB healing site. We recently identified a putative NHEJ repair mechanism in *Streptomyces ambofaciens*. Among the NHEJ-like genes, we distinguished a set of genes conserved across the *Streptomyces* species, and a set of variable genes likely inherited by horizontal transfer. Strikingly, both gene sets were involved in response to DNA damage treatments [1].

Although the high plasticity of the *Streptomyces* linear chromosome was reported as soon as the first genetic studies, the relative contribution of HR and NHEJ to the stability and evolution of *Streptomyces* replicons remains unknown. Here we show that repair of chromosomal DSBs (induced by heterologous I-*SceI* expression) in the chromosome arms is accompanied by the formation of large deletions. In contrast, DSB healing in the conserved region of the chromosome is associated to mutagenic repair in the absence of chromosome rearrangement (probably counterselected). This mutagenic repair is resulting from NHEJ as shown by DSB repair surveys in mutants deficient for different putative NHEJ actors (Ku, ligases). Homologous recombination is shown to occur between duplicated genes (sigma factor encoding genes, transposases) distributed along the chromosome, leading to chromosomal arm replacement and intense DNA amplification. NHEJ repair occurs between sequences sharing or not microhomologies (up to six nucleotides) and induces chromosomal circularization and the formation of large deletions. Further, the involvement of NHEJ was concomitant with the integration of genetic material at the healing site. These data strongly support that DSB repair drives genome plasticity in *Streptomyces*, and that NHEJ may favor insertion of information from horizontal transfer. These recombination processes could confer a strong capacity to evolve in response to environmental adversity.

References

[1] Hoff G, Bertrand C, Zhang L, Piotrowski E, Chipot L, Bontemps C, Confalonieri F, McGovern S, Lecointe F, Thibessard A, Leblond P. Multiple and Variable NHEJ-Like Genes Are Involved in Resistance to DNA Damage in *Streptomyces ambofaciens*. *Front Microbiol.* 2016 Nov 28;7:1901.