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Pathogen profile

Genetic and physiological determinants of *Streptomyces scabies* pathogenicity

SYLVAIN LERAT, ANNE-MARIE SIMAO-BEAUNOIR AND CAROLE BEAULIEU*

Centre SÈVE, Département de Biologie, Université de Sherbrooke, Sherbrooke, QC, Canada, J1K 2R1

SUMMARY

Common scab is a severe disease worldwide affecting tap root crops and potato tubers. It is caused by soil-borne filamentous bacteria belonging to the genus *Streptomyces*. Streptomycetes usually are saprophytic microorganisms, but a few species have acquired the ability to infect underground plant tissues. The predominant causal agent of potato scab worldwide is *Streptomyces scabies*. The production of phytotoxins called thaxtomins is essential for the virulence of common scab-causing agents. The genes involved in the biosynthetic pathway of thaxtomins and other virulence genes are clustered on a large pathogenicity island. The pathogenicity island can be mobilized and transferred to nonpathogenic relatives, leading to the emergence of new pathogenic streptomycetes. In most pathogenic *Streptomyces* species, thaxtomin A is the predominant form found. The regulation of thaxtomin A synthesis is complex. Although the plant-derived compound cellobiose is now recognized as the inducer of thaxtomin A synthesis at a genetic level, other molecules (including aromatic amino acids and some secondary metabolites) show inhibitory effects on the production of the toxin. This paper is an overview of common scab with a focus on *S. scabies* and its virulence mechanisms.

Taxonomy: *Streptomyces scabies* (Thaxt.) Lambert and Loria; Kingdom Bacteria; Phylum Actinobacteria; Class Actinomycetes; Order Actinomycetales; Family Streptomycetaceae; genus *Streptomyces*; species *scabies* or *scabiei*.

Host range: *Streptomyces scabies* (syn. *S. scabiei*) has a broad host range comprising tuber vegetables and most tap root crops. *Streptomyces scabies* causes common scab on potato (*Solanum tuberosum*), beet (*Beta vulgaris*), carrot (*Daucus carota*), parsnip (*Pastinaca sativa*), radish (*Raphanus sativus*), rutabaga (*Brassica napobrassica*) and turnip (*Brassica rapa*).

Disease symptoms: Common scab symptoms appear as randomly distributed shallow, raised or deep-pitted corky lesions. Their size and colour are quite variable, but lesions typically are brown with a diameter of a few millimetres. No above-ground symptoms disclose the presence of the disease as aerial tissues of scab-infected plants remain healthy. *Streptomyces scabies* also inhibits the growth of seedlings in monocot and dicot plants.

Useful websites: http://www.sanger.ac.uk/Projects/S_scabies, http://www.potatodiseases.org/scab.html, http://www.uri.edu/ce/factsheets/sheets/potatoscab.html

*Correspondence: E-mail: carole.beaulieu@usherbrooke.ca

INTRODUCTION

Common scab is a frequent disease of bacterial origin that can thrive in fields in which root and tuber vegetables are grown. The predominant causal agent of potato scab is *Streptomyces scabies*. It belongs to a wide group of filamentous Gram-positive soil bacteria (Fig. 1A) that are essentially saprophytic microorganisms. Nevertheless, *S. scabies* is one of the few members of actinomycetes that is a plant pathogen. Common scab is characterized by visible lesions on the surface of various root and tuber vegetables (Fig. 1B). Symptoms can emerge as shallow, raised or deep-pitted corky lesions, depending on various environmental conditions (Goyer *et al*., 1996). The occurrence of common scab in the field does not usually alter crop yields and the consumption of scab-infected food may not threaten human health. However, as the quality of crops, such as potato, depends on their general appearance, the degree of infection by common scab pathogens directly affects their market value. For instance, the incidence of common scab on potato tubers has been found to generate economic losses of around 15% in Quebec, Canada (Hill and Lazarovits, 2005).

The virulence of pathogenic *S. scabies* strains is essentially dependent on their capacity to produce a family of phytotoxins called thaxtomins (King *et al*., 1989). These secondary metabolites are 4-nitroindol-3-yl-containing 2,5-dioxopiperazines, consisting of cyclized nitro-tryptophan and phenylalanine (the biosynthetic pathway of thaxtomins has been reviewed by Loria *et al*., 2006). The dominant form of thaxtomin produced by *S. scabies* is thaxtomin A (King *et al*., 1992; Fig. 2), although phytotoxicity has also been reported for other thaxtomins (Hiltunen

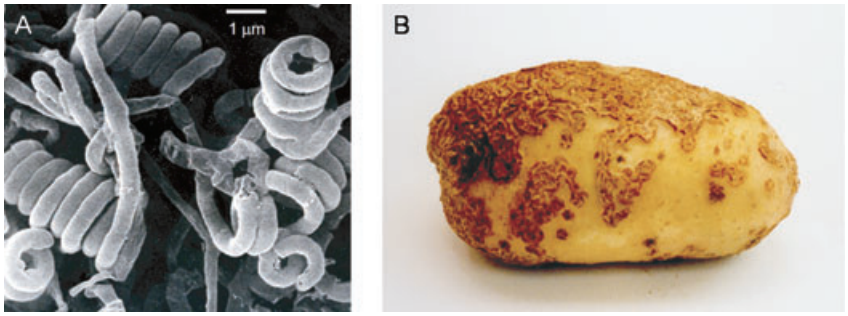

Fig. 1 (A) Filamentous mycelium of *Streptomyces scabies* observed by electron microscopy. Life cycle eventually evolves to the formation of spores borne in spiral chains. (B) Common scab lesions on a potato tuber.

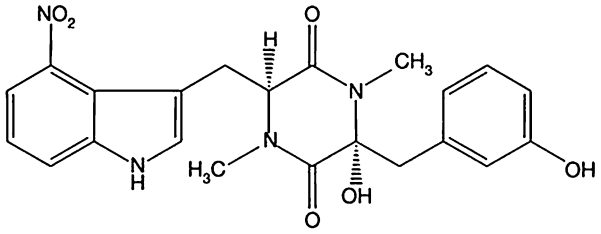

Fig. 2 Schematic representation of thaxtomin A, the major phytotoxin produced by *Streptomyces scabies*.

et al., 2006; King and Lawrence, 2001). Recently, it has been shown that thaxtomin A biosynthesis is induced by the presence of the plant polysaccharides cellobiose and cellotriose (Johnson *et al*., 2007; Wach *et al*., 2007). Cellobiose binds a regulatory protein that upregulates the genes of the biosynthetic pathway of the toxin (Joshi *et al*., 2007b). However, the presence of cellobiose only weakly induces thaxtomin production when the bacterium is grown in minimal medium. Previous work has also reported weak thaxtomin A production in the presence of suberin, a plant polymer covering the surface of potato tubers (Beauséjour *et al*., 1999). A combination of suberin and the thaxtomin inducer cellobiose generates the production of large amounts of the phytotoxin by *S. scabies* grown in minimal medium (S. Lerat *et al*., unpublished data). The role of suberin in thaxtomin biosynthesis needs to be elucidated, but it is hypothesized that suberin stimulates secondary metabolism and thus might favour thaxtomin production (Lauzier *et al*., 2008).

The effect of thaxtomins on plant physiology has been investigated in several plant species. However, the mechanisms of action of the toxins have been only partially identified to date. The pathogens are thought to derive carbohydrates from expanding underground plant tissues through the inhibition of cellulose synthesis (Fry and Loria, 2002; Scheible *et al*., 2003). Nonetheless, the presence of thaxtomin has also been shown to trigger plant defence mechanisms. An early plant response to thaxtomin A in *Arabidopsis thaliana* is Ca^{2+} influx (Duval *et al*., 2005; Errakhi *et al*., 2008; Tegg *et al*., 2005). Calcium is a key messenger in the reaction of plants challenged by pathogens. In *A. thaliana* culture cells, the calcium-mediated plant response to thaxtomin A ultimately leads to programmed cell death (Duval *et al*., 2005; Errakhi *et al*., 2008). Moreover, experiments conducted on tobacco and *A. thaliana* have shown that both *S. scabies* and thaxtomin A elicit the production of scopoletin, a plant defence phytoalexin (S. Lerat *et al*., unpublished data). Interestingly, when the pathogenic agent was grown in a thaxtomin-inducing growth medium, the presence of scopoletin caused a drastic decrease in toxin synthesis (S. Lerat *et al*., unpublished data).

Pathogenic *Streptomyces* species do not show a high level of host specificity under controlled conditions. Leiner *et al*. (1996) reported the effect of inoculation with virulent *S. scabies* strains on the seedlings of 14 crop plants, including monocot and dicot species. The presence of the pathogenic bacterium negatively altered shoot growth in 11 of the species tested. This is not surprising as the target of thaxtomins is a universal component of plant cell walls (i.e. cellulose). Nevertheless, the range of hosts having a propensity to common scab infection under field conditions appears to be restricted to a limited number of agricultural crops (Goyer and Beaulieu, 1997). Moreover, a few potato cultivars are recognized as resistant or moderately sensitive to the disease (Hiltunen *et al*., 2005). Therefore, the host infection process that leads to common scab under natural conditions appears to be governed by complex plant–microbe interactions.

COMMON SCAB: A DISEASE ON THE SPREAD

The causal agent of potato common scab was first identified in North America in the late 19th century (Thaxter, 1892). A review of the recent scientific literature reveals that this disease is now present worldwide, wherever potatoes are cultivated. In addition to the predominant and well-studied species *S. scabies*, other *Streptomyces* species are recognized as common scab-causing agents (Beaulieu *et al*., 2008). The isolation of actinomycetes from infected potato tubers has led to the discovery of new or unidentified pathogenic agents (Bouchek-Mechiche *et al*., 2000; Miyajima *et al*., 1998; Park *et al*., 2003; Wanner, 2006, 2007). The exhaustive list of common scab-causing agents contains various, not closely related *Streptomyces* species. Worthy of mention are

S. turgidiscabies and *S. acidiscabies*, which appear to be the most widely distributed scab pathogens after *S. scabies*. They can be distinguished from each other by differences in morphology (Lambert and Loria, 1989a, b; Miyajima *et al*., 1998), carbon source utilization (Miyajima *et al*., 1998) and 16S rRNA sequence (Bouchek-Mechiche *et al*., 2000; Lehtonen *et al*., 2004). It is assumed that, in most species, pathogenicity was acquired after the mobilization and lateral transfer of genetic material from common scab-causing strains to saprophytic recipient strains (Kers *et al*., 2005).

The genes conferring pathogenicity are generally clustered within a large pathogenicity island (PAI), which represents a unique report in Gram-positive bacteria (Kers *et al*., 2005). Among them are genes involved in thaxtomin biosynthesis, as well as open reading frames showing strong similarities to virulence genes associated with other pathogenic organisms. In an elegant study aimed at the investigation of the genetic variability of common scab-causing agents, Wanner (2006) tested for the presence of three marker genes of the PAI in the genome of about 100 isolates. The genes under investigation were a gene involved in thaxtomin biosynthesis (*txtAB*), a necrosis gene (*nec1*) and a tomatinase (*tomA*). All isolates that contained the *txtAB* gene showed pathogenicity on potato or radish. However, some pathogenic isolates lacked the presence of one or both of the *nec1* and *tomA* genes. The absence of the *nec1* gene has been reported previously in some pathogenic *S. scabies* strains isolated in Finland (Kreuze *et al*., 1999). More recently, Flores-Gonzáles *et al*. (2008) have shown that the *nec1* gene is missing from one-half of the pathogenic *Streptomyces* isolates obtained from infected potatoes. This implies that, unlike the *txtAB* genes, the *nec1* and *tomA* genes are not essential for pathogenicity. Consequently, polymerase chain reaction (PCR)-based techniques targeting the *txtAB* operon (or other genes of the synthetic pathway of thaxtomins) can be legitimately used as the most robust diagnostic tools for the detection of common scab-inducing pathogens in biological and soil samples (Flores-Gonzáles *et al*., 2008; Qu *et al*., 2008).

ORGANIZATION OF VIRULENCE-RELATED GENES IN *S. SCABIES*

Evidence for the existence of a PAI was established in *S. turgidiscabies* (Kers *et al*., 2005). At the very least, parts of the PAI were shown to be conserved among pathogenic *Streptomyces* (Kers *et al*., 2005; Wanner, 2006). In *S. turgidiscabies*, the size of the PAI has been estimated to be between 325 and 660 kb. However, the public release of the complete genome of *S. scabies* (Sanger Institute, http://www.sanger.ac.uk/Projects/S_scabies/) revealed a curious feature regarding the organization of PAI in this species. In *S. scabies* strain 87.22, typical genes of PAI are found in two remote regions of the bacterial chromosome. For instance, the *txtA* and *nec1* genes are over 4900 kb distant (the whole genome is *c*. 10 149 kb). Interestingly, this physical separation also mirrors a partition of functions.

Genes associated with toxin production are clustered in the first section of the PAI, which we will call the 'toxicogenic region' (http://www.sanger.ac.uk/Projects/S_scabies; estimated coordinates *c*. 3596–3653 kb; G + C content of 68%). All genes shown to be involved in thaxtomin biosynthesis are found in this region (Table 1). These genes are *txtAB* (Healy *et al*., 2000), *txtC* (Healy *et al*., 2002), *nos* (Kers *et al*., 2004) and *txtR* (Joshi *et al*., 2007b). They code for a nonribosomal peptide synthase (cyclization of the dipeptide), a cytochrome P450 monooxygenase (hydroxylation of the cyclic dipeptide), a nitric oxide synthase (nitration of the tryptophan moiety is essential for the toxicity of thaxtomins) and a cellobiose-binding regulatory protein, respectively. A schematic representation of the organization of these genes in *S. scabies* has been supplied by Joshi *et al*. (2007b). An open reading frame coding for a protein sharing 44% similarity with a putative phage integrase in *Streptomyces* sp. Mg1, and separated from *nos* by only 2634 bp, is apparently the only complete mobile genetic element associated with this region. The second segment of the PAI, which we will call the 'colonization region', contains considerably more genes (http://www.sanger.ac.uk/Projects/S_scabies; estimated coordinates *c*. 8471–8581 kb; G + C content of 68.5%). This chromosomal region includes genes such as *nec1* and *tomA* which are not essential to pathogenicity, but play a significant role in virulence. Nec1 and TomA may play a role in the infection process through the suppression of plant defences (Joshi *et al*., 2007a; Seipke and Loria, 2008). Four open reading frames showing similarities with transposases are found in the close vicinity of the *nec1* gene. The presence of genes coding for esterase-like proteins in the same region also deserves to be mentioned, as extracellular esterase activity was measured in *S. scabies* (Beauséjour *et al*., 1999; Schottel *et al*., 1992) and some esterases are thought to play a role in the degradation of suberin, which can act as a physical barrier against microbial invasion (Kolattukudy, 1980). Table 1 presents a list of genes associated with the toxicogenic and colonization regions.

EFFECT OF AROMATIC AMINO ACIDS ON *S. SCABIES* VIRULENCE

Streptomyces scabies possesses the capacity to produce melanoid pigments, as do several bacteria, fungi, plants and animals (Sánchez-Ferrer *et al*., 1995). Melanin is a pigment synthesized from the amino acid tyrosine by a multifunctional tyrosinase enzyme (Bell and Wheeler, 1986). In *S. scabies*, the mechanisms leading to melanin production and thaxtomin synthesis are somewhat correlated. Beauséjour and Beaulieu (2004) generated *S. scabies* mutants deficient in melanin biosynthesis. Inter-

Table 1 Examples of the main functions* associated with the open reading frames (ORFs) present in *Streptomyces scabies* pathogenicity island.

Toxicogenic region			Colonization region		
Putative function of the protein-coding gene	Name	Position† (ORF length, bp)	Putative function of the protein-coding gene	Name	Position† (ORF length, bp)
Gene regulation			Gene regulation		
AraC family regulatory protein	*txtR*	3 610 920 (834)	LacI family regulatory protein		8 539 752 (912)
Mobile genetic elements			Mobile genetic elements		
Phage integrase family protein		3 617 834 (1224)	Transposase		8 515 735 (1191)
Phytotoxic compound biosynthesis			Virulence		
Cytochrome P450	*txtC*	3 598 108 (1188)	Necrosis protein	*nec1*	8 514 341 (555)
MbtH-like protein‡		3 600 056 (198)	Tomatinase	*tomA*	8 542 763 (1602)
Thaxtomin synthetase B	*txtB*	3 600 343 (4467)	Hydrolytic enzymes		
Thaxtomin synthetase A	*txtA*	3 604 857 (4377)	Glycosyl hydrolase		8 528 829 (1260)
Nitric oxide synthase	*nos*	3 615 200 (1173)	Glycosyl hydrolase		8 530 643 (2418)
Bacteriocin biosynthesis			Glycosyl hydrolase		8 541 164 (1434)
Lantibiotic precursor§		3 630 960 (171)	Esterase/lipase		8 509 360 (906)
Lantibiotic dehydratase-like§		3 631 341 (3006)	Epoxide hydrolase		8 575 654 (714)
Lanthionine synthetase C-like§		3 634 343 (1233)	Detoxification/stress resistance		
Aerial mycelium development			β-Lactamase domain-containing protein		8 490 519 (1365)
Sensor histidine kinase¶		3 638 794 (1305)	Rhodanese domain-containing protein		8 493 161 (5760)
Roadblock/LC7 domain-containing protein¶		3 640 095 (417)	Bacitracin resistance protein		8 581 305 (876)
			Transport		
RarC-like protein¶		3 640 538 (333)	Cellobiose ABC transporter permease		8 535 066 (822)
RarD-like protein¶		3 640 896 (573)	Cellobiose ABC transporter permease		8 537 128 (1230)
Cytochrome P450¶		3 641 465 (1323)	Cellobiose ABC transporter permease		8 535 977 (987)
			Sugar ABC transporter permease		8 551 858 (840)
			ABC-type antimicrobial peptide transport system		8 502 763 (780)

*The protein-coding gene sequence was predicted using the GeneMark.hmm for Prokaryotes program (Version 2.4; Lukashin and Borodovsky, 1998) and protein function was determined using the BLASTP program (National Center for Biotechnology Information).

†Position in the *S. scabies* genome sequence release by the Sanger Institute (http://www.sanger.ac.uk/Projects/S_scabies/).

‡MbtH-like proteins are a family of proteins encoded by genes often found in clusters responsible for the biosynthesis of peptide antibiotics. There is no experimental evidence that this protein is necessary for thaxtomin synthesis.

§Cluster containing genes encoding proteins involved in the biosynthesis of lantibiotic. There is no experimental evidence that this cluster allows bacteriocin synthesis in *S. scabies*.

¶Gene cluster similar to *rarA-E* cluster of *Streptomyces griseus* (Komatsu *et al.*, 2003).

estingly, thaxtomin A production was negatively affected in most of these mutants, suggesting that some regulatory or biosynthetic pathways leading to toxin synthesis and melanogenesis could be connected. Nevertheless, as thaxtomin synthesis in the melanin-deficient mutants was not totally abolished, pathogenicity tests performed on potato tubers showed that bacterial virulence was not reduced in all melanin-deficient mutants (Beauséjour and Beaulieu, 2004). Furthermore, all mutant strains retained the capacity to sporulate under standard conditions, but their growth and sporulation capacities showed higher sensitivity to various stresses than did the wild strain, suggesting that the synthesis of melanin and thaxtomins may be linked to the stress response in *S. scabies*.

Streptomyces scabies also has the ability to synthesize the plant growth phytohormone indole-3-acetic acid (IAA) using tryptophan as a precursor (Manulis *et al.*, 1994). This trait is common amongst soil-inhabiting bacteria. The stimulating effect on plant growth of some rhizobacteria relies on their capacity to synthesize auxins (Patten and Glick, 1996). In *S. scabies*, IAA synthesis seems to be regulated by tryptophan availability, as extracellular IAA production increases with tryptophan concentration (G. Legault *et al.*, unpublished data, Université de Sherbrooke). When expressed as a function of tryptophan concentration, bacterial thaxtomin A and IAA display opposite profiles of production (Fig. 3). The role of bacterial biosynthesis of auxins in the interaction between *S. scabies* and potato needs to be investigated further, but auxins show remarkable effects on common scab. Evidence of reduced common scab incidence on potatoes was observed following foliar applications of auxin analogues in glasshouse and field experiments (McIntosh *et al.*, 1981, 1982). However, auxin treatments were associated with low yields of marketable tubers. Recently, in an attempt to elucidate the mechanisms whereby foliar sprays of auxin analogues reduce common scab severity, Tegg *et al.* (2008) reported the accumulation of the synthetic auxin 2,4-dichlorophenoxyacetic acid in tubers of treated plants. This accumulation translated into an enhanced tolerance to thaxtomin A. Auxins had no toxic effect on *S. scabies*, but 2,4-dichlorophenoxyacetic acid (at a

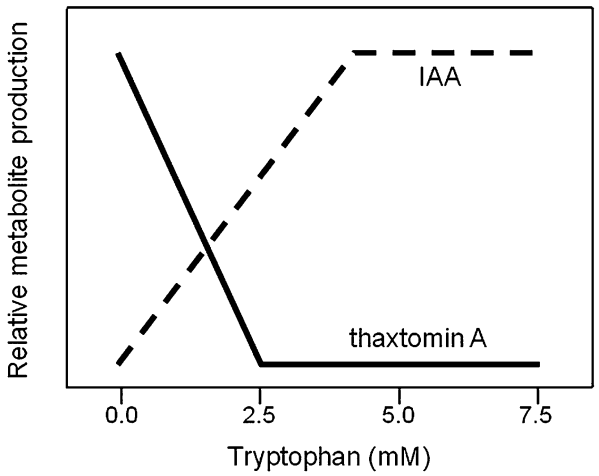

Fig. 3 Effect of tryptophan on the relative production of thaxtomin A and indole-3-acetic acid (IAA) in *Streptomyces scabies* (strain EF-35) grown in minimal medium. Increasing tryptophan concentrations totally inhibited thaxtomin A biosynthesis, but stimulated IAA production.

concentration of 1 mM) showed inhibitory effects on thaxtomin production (Tegg *et al*., 2008).

Although tryptophan and phenylalanine are biosynthetic precursors of thaxtomins, the exogenous supply of aromatic amino acids in the culture medium induces the inhibition of thaxtomin biosynthesis. In a study on the regulation of thaxtomin synthesis, Lauzier *et al*. (2002) investigated the effect of amino acids on toxin production. Aliphatic amino acids had no significant effect on thaxtomin A production at a concentration of 2.5 mM or less. However, the presence in the growth medium of *S. scabies* of the three aromatic amino acids, tryptophan, phenylalanine and tyrosine, at a concentration of 2.5 mM totally inhibited or greatly reduced the production of thaxtomin A (Lauzier *et al*., 2002). These results were unexpected as examples of the inhibition of a biosynthetic molecule by its own precursors are rare. No clear explanation has yet been offered to elucidate such a regulatory mechanism. Tryptophan and other aromatic amino acids therefore appear to be key molecules in the metabolism and virulence process of *S. scabies*.

PERSPECTIVES

This article is an attempt to describe concisely the most recent knowledge on the pathogenicity of *S. scabies*, the major pathogenic agent responsible for common scab. The mechanisms of virulence may at first appear to be straightforward, as the pathogenic agent that detects the presence of a host plant excretes a phytotoxin that eventually targets a plant function. However, the events leading to toxicity are complex and represent an exciting challenge for researchers. Moreover, in spite of the knowledge accumulated over the past 30 years, no efficient method is yet available to control the disease in the field. In addition, the damage caused to crops by common scab is greater than ever. The fact that the genes responsible for pathogenicity can disseminate by lateral transfer implies that common scab may theoretically develop in any streptomycetes-bearing soil, propagating the disease to new niches. However, several avenues can be followed to find solutions for the biocontrol of common scab (for example, Beauséjour *et al*., 2003; Hiltunen *et al*., 2009; Liu *et al*., 1995).

Most of the research which is presently being conducted is essentially focused on the bacterial pathogenicity mechanisms. This approach minimizes the importance of the plant in this host–microbe interaction, and more attention should be given to the plant partner. Common scab-resistant cultivars are of specific relevance as they may help to identify the physiological events restraining the development of the plant pathogens.

The close link between tryptophan, auxins and thaxtomins, possibly caused by chemical similarities, is also of particular interest. Tegg *et al*. (2005) suggested the possible competition between auxin and thaxtomin A for auxin receptors. Foliar sprays of auxin analogues are accompanied by tuber growth issues, but have been proven to be efficient in limiting the impact of the pathogenic agents. Research into the hormonal aspects may improve the control of the disease in the field.

A comprehensive understanding of the virulence mechanisms of common scab-causing agents still remains a promising research avenue. The complete sequencing and recent annotation (Loria *et al*., 2008) of the *S. scabies* genome opens up a new area. Today's molecular tools, such as DNA microarray techniques, are powerful and should eventually help to unravel the regulation mechanisms triggering pathogenicity.

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