Gorovits et al. Phytopathology Research (2019) 1:20
https://doi.org/10.1186/s42483-019-0028-4

Phytopathology Research

REVIEW Open Access

Taking advantage of a pathogen: understanding how a virus alleviates plant stress response

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Abstract

The simplicity of *Tomato yellow leaf curl virus* (TYLCV) genome, encoding six proteins only, contrasts with the complexity of its impact on tomato plants. In this review, we discuss our understanding of how TYLCV proteins establish infection, and how the virus suppresses the effects of several abiotic stresses. TYLCV counteracts cell death induced by other factors, such as inactivation of HSP90 functions. Suppression of plant death is associated with the inhibition of the ubiquitin 26S proteasome degradation and with a deactivation of the heat shock transcription factor HSFA2 pathways. In order to ensure its own life cycle and spread, TYLCV protects the infected host from various unfriendly stresses, and this property can be exploited to protect crops from environmental stresses.

Keywords: Biotic and abiotic stresses, Begomoviruses, Cell death, Suppression of plant cell death

Background

In tropical and sub-tropical countries, tomatoes grown in the field in the spring and summer, are frequently exposed to temperatures of 40 ° C (and higher), often in combination with *Tomato yellow leaf curl* virus (TYLCV) infection. This whitefly-transmitted begomovirus reprograms the cell cycle of mature plant cells, interacting with host factors to create a permissive environment for viral replication (Hanley-Bowdoin et al. 2013). However, to ensure a successful long-term infection cycle, geminiviruses must restrain their destructive effect on the host cells and prevent drastic plant responses. On the other hand, high temperatures involve reprogramming of signal transduction components, transcription factors and proteins associated with the metabolism of stress-generated reactive oxygen species, ROS (Grover et al. 2013). Traditionally, individual plant stress factors have been studied as isolated stimuli that trigger signaling pathways. However, it is clear that both biotic and abiotic stress pathways are inextricably linked in a broad network of molecular interactions. The plant lines with improved stress tolerance should be tested under the full range of stress combinations that are likely to occur in the field, rather than for each stress individually.

TYLCV infection inactivates cellular heat shock response. In TYLCV infected tomatoes, a significant reduction in the levels of transcription and translation of the heat-inducible genes leads to reduced cell death. Recently, we described the suppression of host cell death, induced by inhibition of HSP90 and its co-chaperone SGT1, in tomato plants infected by TYLCV (Moshe et al. 2016). On the other hand, elevated temperatures interfere with plant-pathogen interactions, often compromising R gene-mediated disease responses, including the hypersensitive response (HR) (Zhu et al. 2010). Comparing the heat shock (HS)-dependent activation profiles of the main heat response players such as HSFs and HSPs in TYLCV-infected and uninfected tomatoes showed that the constitutively expressed HS transcription factor HSFA1 and the heat-inducible forms HSFA2 and HSFB1 accumulate to high levels (Scharf et al. 2012). HSFs may act as molecular sensors to detect the presence of ROS such as H_2O_2 and activate downstream stress-responsive genes such as *Apx1/2*, *Hsp17* and others, allowing plants to respond to different environmental conditions (Yoshida et al. 2011). Stable

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HSFA2 confers a stress resistance phenotype while maintaining yield productivity.

It might be possible to increase the heat tolerance of TYLCV-susceptible plants by pre-inoculating (by agroinfection) seedlings with a TYLCV symptomless mutant lacking 20 amino acids near the N-terminus of the CP (Peretz et al. 2007), and therefore not transmissible by whiteflies, before planting in the field. We expect that the mutant will have the same capacity to suppress the HS response and to increase heat tolerance as the wild type virus.

Observed changes in plant stress responses against abiotic/heat and biotic/TYLCV stresses are discussed in this review.

The interactive effects of biotic and abiotic stresses on plants

Sessile plants may be exposed to numerous environmental stresses during their growth. In natural conditions, many abiotic (e.g. heat and drought) and biotic (e.g. viral and fungal infections) stresses occur simultaneously. Plants have developed specific mechanisms that allow them to detect environmental changes and respond to complex stress conditions, minimizing damage while conserving valuable resources for growth and reproduction. Different stress factors occurring in combination can be considered additive, when these damage factors pile up, or are interactive, when a first stress alters the response to a second stress (Niinemets 2010).

The results of simultaneous biotic and abiotic stress investigations indicate that abiotic stresses, particularly heat and drought, enhance plant susceptibility to pathogens, provoking severe yield losses. For example, sorghum and the common bean subjected to drought showed a higher susceptibility to the fungus *Macrophomina phaseolina* (Mayek-Perez et al. 2002). In *Nicotiana benthamiana* and *Arabidopsis thaliana*, the hypersensitive (HR) and R-gene mediated defense responses to *Pseudomonas syringae* and viral elicitors are compromised at high temperatures, allowing the increased growth of these pathogens (Wang et al. 2009). In wheat, increasing temperatures observed over a six-year period correlated with enhanced susceptibility to the fungus *Cochliobolus sativus* (Sharma et al. 2007).

The interplay between heat stress and viral pathogens is of special interest. At high temperatures, the collapse of the *N. tabacum* N gene-mediated *Tobacco mosaic virus* (TMV) resistance was caused by heat-induced conformational changes of the plant R protein and was associated with downregulation of NADPH oxidase and superoxide, and stimulation of dehydroascorbate reductase (Király et al. 2008). Mild increases in temperature also compromised the R gene-mediated HR following expression in *N. benthamiana* of *Potato virus X* (PVX) coat protein (CP) or of TMV helicase (Wang et al. 2009) . At high temperatures, *Tomato spotted wilt virus* (TSWV) suppressed the TSWV-mediated HR in pepper plants (*Capsicum annuum*) (Moury et al. 1998). A combination of heat, drought and *Turnip mosaic virus* (TuMV) infection was investigated in *Arabidopsis* (Prasch and Sonnewald 2013). A significant reduction in biomass was associated with every single stress, which was exacerbated when the different stresses were applied together, especially under a combination of virus and heat stresses. Moreover, heat alone or heat and drought increased the susceptibility of *Arabidopsis* plants to virus infection. The increased susceptibility was claimed to reside in an altered expression of components of the signal transduction pathway and/or in a modified metabolite signaling.

TYLCV is able to alleviate plant cell death induced by other factors

TYLCV does not induce a hypersensitive response and cell death upon whitefly-mediated infection of virus-susceptible tomato plants, until diseased tomatoes become senescent (Gorovits and Czosnek 2007). The way begomoviruses evade the plant defenses and interfere with the cell death pathways is still poorly understood. Using tomato plants, we have shown that cell death was induced by the inactivation of HSP90 as well as by silencing the genes *Hsp90* and *Sgt1* (HSP90 co-chaperone), which led to the accumulation of damaged ubiquitinated proteins. TYLCV infection was able to alleviate cell death and these accompanying effects (Moshe et al. 2016). The key cellular chaperone HSP90 plays an essential role in the interaction, assembly and maintenance of the 26S proteasome. Functional loss of HSP90 upon incubation with geldanamycin (GDA) causes the dissociation of the 26S proteasome and a significant decrease of its peptidase activity in yeast (Imai et al. 2003) and plant (Nishizawa-Yokoi et al. 2010) cells. Simultaneously, inactivation of the HSP90 machinery leads to the activation of the heat stress transcription factors HSFA2 and HSFB1 (Nishizawa-Yokoi et al. 2010). TYLCV infection down-regulated cell death phenotype, induced by the inhibition of HSP90. Furthermore, the virus impaired the signal transduction pathways leading to cell death, such as ubiquitin–26S proteasome system UPS (Fig. 1) and HSF-regulated transcription of essential cellular stress genes (Moshe et al. 2016). The effect of *Hsp90*/*Sgt1* gene silencing was mitigated by TYLCV infection: instead of becoming even more diseased, the infected plants showed a dramatic diminution in the magnitude of cell death. It has to be noted that TYLCV infection did not suppress the silencing of *Hsp90* and *Sgt1* (Moshe et al. 2016). Therefore, TYLCV not only does not induce HR and cell

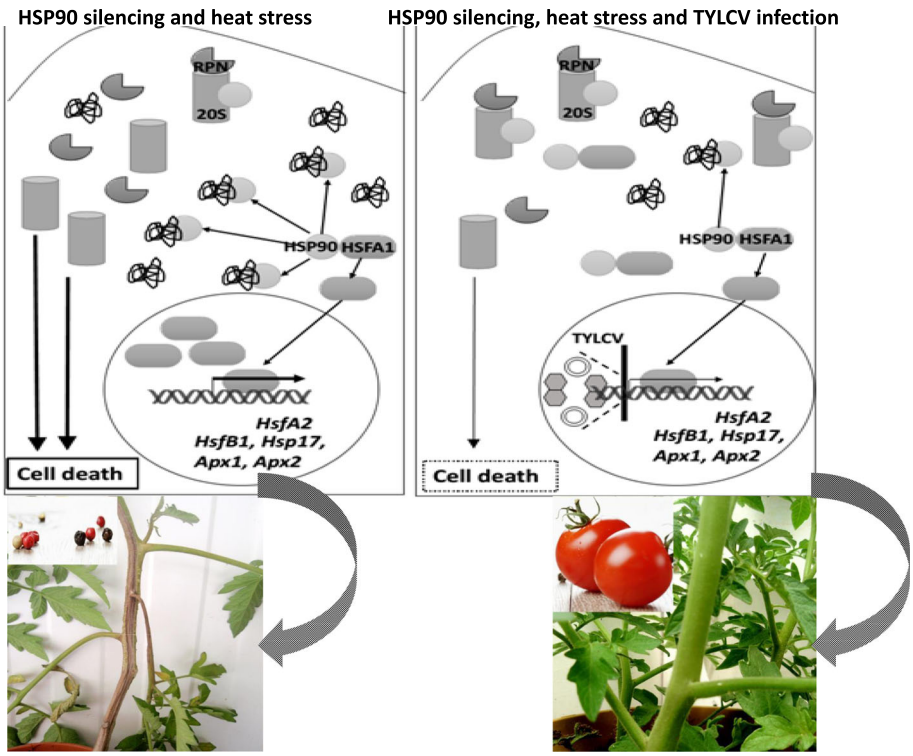

Fig. 1 Summary of the key processes of stress response regulation by HSP90 in tomato plants, and down-regulation by TYLCV infection. Functional loss of the cellular chaperone HSP90 causes the dissociation of the 26S proteasome and a significant decrease of its peptidase activity, consequently, to an increase in the level of ubiquitinated proteins and cell death signs. The inhibition of the 26S proteasome stimulated the expression of heat-inducible genes, including transcription factor HSFA2, in the plant and mammals cells. The involvement of HSP90 in the regulation of signal transduction via HSFA2 activation was demonstrated in several plant species, including tomatoes (Hahn et al. 2011). We have shown that in tomatoes, the levels of HSFA2 were rather low in leaves of uninfected tomato plants. The amounts of HSFA2 greatly increased upon heat stress in uninfected tissues, and much less in TYLCV-infected leaves. The inhibition of HSP90 activity caused an additional increase in HSFA2 expression. Subsequent TYLCV infection reduced HSFA2 levels as well as the expression levels of *HsfB1*, *Hsp17, Apx1,* and *Apx2* (Moshe et al. 2016). TYLCV infection (represented as virions and viral DNA) suppresses HSP90-dependent 26S proteasome inactivation, cell death and HSFA2 signal transduction pathways, resulted in wealthy growth and yielding of tomatoes

death in the infected tomatoes by itself, but it is able to suppress these events, induced by the other stresses, such as inactivation of HSP90 signaling (Fig. 1).

The interplay of heat and TYLCV stresses in tomatoes

Increasing temperatures involve the reprogramming of signal transduction components, transcription factors and proteins associated with the metabolism of stress-generated reactive oxygen species (ROS; reviewed in Grover et al. 2013 and references therein). Transcript profiling of tomato plants showed that genes affected by high temperatures included those encoding for heat shock proteins (HSPs), osmolytes, enzymes that affect the membrane fluidity and enzymes involved in ROS homeostasis (Frank et al. 2009). Further analysis suggests that high temperature response requires a coalition of pathways that culminate in the activation/synthesis of heat stress transcription factors (HSFs) and accumulation of HSPs. Plants possess a larger number of *Hsf* genes than animals, leading to the hypothesis that HSFs have gained additional functions in plants (von Koskull-Döring et al. 2007). Support for this hypothesis comes from the overexpression of HSFA2 in transgenic *Arabidopsis*, which resulted in an increased tolerance to combined light and heat (Nishizawa et al. 2006). Moreover, different biotic stresses induce HSF expression indicating that they may also play a role in pathogen defense (von Koskull-Döring et al. 2007).

In tomato cultures subjected to heat stress, two heat-inducible forms, HSFA2 and HSFB1, complement the constitutively expressed transcription factor HSFA1. Because of its stability, HSFA2 accumulates to high levels during prolonged heat stress and recovery from stress. It tightly regulates the expression of the scavenging enzymes ascorbate peroxidase (APX) gene family, which may play a major role in removing intercellular H_2O_2 and preventing ROS overproduction (Zhang et al. 2009).

The stress combination of hot weather and TYLCV infection leads to severe disease symptoms and yield losses

in TYLCV-susceptible tomatoes. One of the major intracellular effect of simultaneous heat and virus stresses was the development of large protein aggregates containing TYLCV proteins and DNA together with cellular stress proteins, such as HSPs (Anfoka et al. 2016). The appearance of such virus-induced large protein aggregates is a feature of a successful virus invasion in TYLCV susceptible tomatoes (Gorovits et al. 2013). The maintenance of cellular chaperones in the aggregated state, even after recovery from heat stress, prevents the circulation of free soluble chaperones, causing an additional decrease in the efficiency of stress response (Anfoka et al. 2016).

The combined effect on tomato plants of TYLCV infection and heat stress was investigated by following the expression of the prevailing transcription factor HSFA2 and HSFA2-dependent genes (*Hsp17*, *Apx1*, *Apx2*), induced by high temperatures. When TYLCV-infected leaves were subjected to heat, the increase in the amounts of HSFA2 and HSFA2-dependent genes was less pronounced versus un-infected plants. Special interest aroused during the recovery period, when tomato leaf samples were returned to room temperature (23 °C–25 °C) after heat shock, *HsfA2*, *HsfB1*, *Hsp17*, *Apx1*, *Apx2* and *Hsp90* genes were still less expressed in leaves of TYLCV-infected plants than in uninfected tomatoes.

To advance the understanding of how TYLCV is able to down-regulate the heat-induced activation of HSFA2 and HSFA2-dependent genes' expressions, the cellular localization of HSFA2 was examined. HSFs exist as inactive proteins mostly found in the cytoplasm, while heat treatment causes HSFA2 activation with translocation to the nucleus, where it binds to its target sequences (HSEs) present in the promoter regions of HS genes (Scharf et al. 2012 and references therein). In the cells of TYLCV infected tomato leaves, HSFA2 partially remained in the cytoplasm, even under prolonged heat stress. All the six TYLCV proteins were able to interact with tomato HSFA2 in vitro, moreover, viral CP developed complexes with HSFA2 in nuclei (Anfoka et al. 2016). Capturing HSFA2 by viral proteins could suppress the transcriptional activation of heat stress response genes (Fig. 1).

Suppression of heat stress response in infected TYLCV-susceptible (S-967) and -resistant (R-GF967) tomatoes

The efforts of scientists and breeders have resulted in the development of commercial tomato lines tolerant to TYLCV. Tomato breeding lines were developed from the same initial cross between a wild tomato TYLCV-resistant accession and a cultivar with excellent horticultural traits: one is susceptible to TYLCV (S, 967), the other is resistant to the virus (R, GF967) (Anfoka et al. 2016). The infected symptomatic S tomatoes accumulated large amounts of virus during prolonged infection, while the asymptomatic R plants contained less, but still substantial amounts of TYLCV (Gorovits et al. 2013). TYLCV presence in R tomatoes does not influence plant growth, fruit ripening and fruit quality. TYLCV-infected S-967 and R-GF967 tomatoes were grown at different regimes: normal (25 °C) and high (40 °C–45 °C) temperatures. A heat-induced increase in the amounts of heat stress-dependent proteins was observed in non-infected S-967 and R-GF967 tomatoes (Anfoka et al. 2016). In infected tomatoes, the amounts of HSFA2, HSP90, HSP100/ClpB decreased. The activation of HSFA2, HSP90, HSP100/ClpB was less pronounced in line S-967, which contained large amounts of virus, than in line R-GF967. However, even in R-GF967 plants, heat-induced protein expression was diminished at the late stages of infection, when virus started to be detectable. Hence, there is a correlation between TYLCV accumulation and a decline in the efficacy of plant heat stress response.

Perspectives of using TYLCV to protect tomato plants against environmental stresses

The down-regulation of heat stress response in infected TYLCV-resistant tomato line R-GF967 allowed us to formulate a seemingly paradoxical procedure to protect tomato plants from extreme heat. Several days before transfer to fields under scorching summer sun, tomato seedlings are pre-inoculated with TYLCV. During the first 6–12 days, enough virus accumulated in the TYLCV-resistant plants in order to weaken the plant response to extreme heat. TYLCV prevents plant death to create a proper environment for its successful replication, thereby alleviating the inhibition of plant growth and flowering due to extreme heat. Indeed, in greenhouse experiments were temperatures reached 45 °C–50 °C, R-GF967 tomatoes collapsed and died after several days. In comparison, TYLCV pre-inoculated R-GF967 plants continued to grow (Fig. 2).

A similar approach of using TYLCV pre-inoculated tomatoes may be applied to achieve an increased tolerance against other environmental stresses; first, against drought, which usually paralleled heat stress. It is also possible to appraise the levels of tomato tolerance to salinity and oxidative stress. There is no doubt that the ability of TYLCV inoculation to protect tomato plants against certain abiotic or biotic stress depends on master regulatory elements involved in an interplay between specific stress combinations. Moreover, the time course of such interplay could be the determining factor in the stress interaction. For example, the capacity of TYLCV to downregulate plant response to several biotic stresses was investigated by using the tomato fungal pathogens

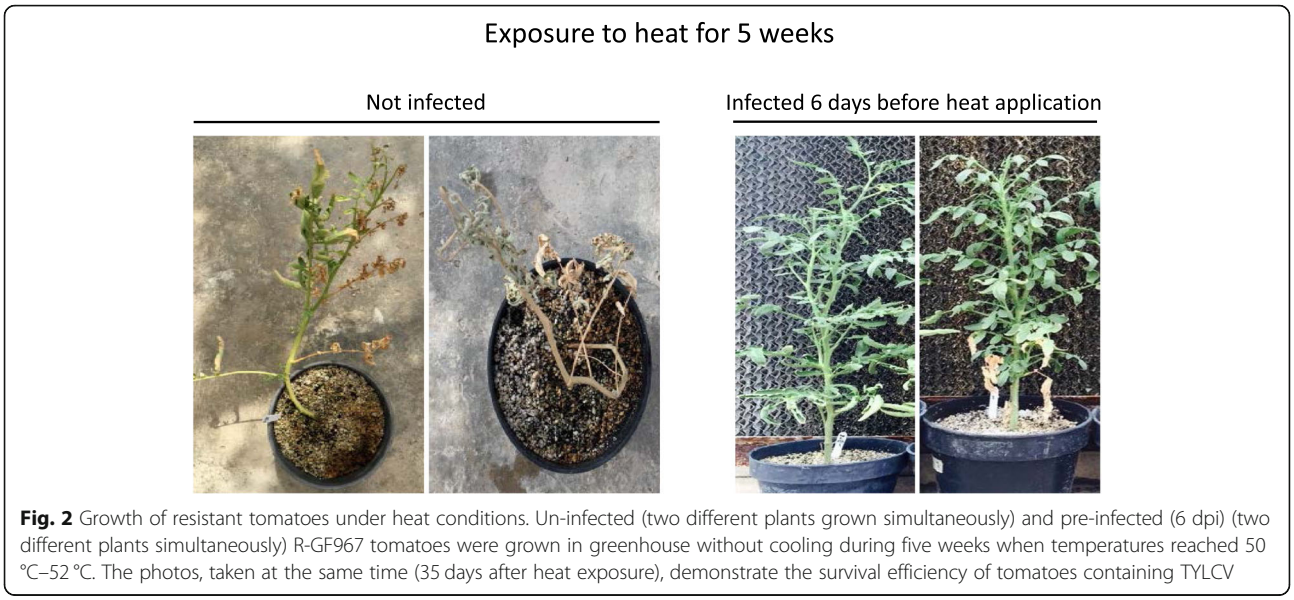

Fig. 2 Growth of resistant tomatoes under heat conditions. Un-infected (two different plants grown simultaneously) and pre-infected (6 dpi) (two different plants simultaneously) R-GF967 tomatoes were grown in greenhouse without cooling during five weeks when temperatures reached 50 °C–52 °C. The photos, taken at the same time (35 days after heat exposure), demonstrate the survival efficiency of tomatoes containing TYLCV

Sclerotinia sclerotiorum and *Botrytis cinerea*. Both fungi are necrotrophic pathogens that attack over 200 different plant species (Elad 1997). The infection is manifested by necrotic areas with extensive fungal growth, giving the characteristic appearance of grey mould. Recognition of the pathogen attack triggers HR in the plant, which includes generation of ROS intermediates and local cell death (Govrin and Levine 2000; Huang et al. 2009). TYLCV pre-inoculated tomatoes were exposed to *S. sclerotiorum* and *B. cinerea* stresses. In general, TYLCV promoted the development of both fungal pathogens; however, reduction of the pathogens' growth was not detected in virus-infected tomato leaves. The exception was during a very restricted period, when the presence of fast replicated virus almost stopped *S. sclerotiorum* spread. What is known to be different in mechanisms of infection by *B. cinerea* versus relative necrotrophic fungi *S. sclerotiorum*? It was demonstrated that *S. sclerotiorum* had a biotrophic phase, which occurred during the initial stages of the disease establishment (Kabbage et al. 2013). Host defense responses, in particular HR, are suppressed as the fungus grows through living tissues. Once the fungus was established, a transition to necrotrophy occurred and host cell death pathways were subverted, inducing apoptosis. This fungal induced-death provides nutrients that were exclusively for the benefit of the fungus. In non-pathogenic mutants, plant controlled cell death via autophagy was observed. If autophagy was blocked, genetically or pharmacologically, resistance was compromised and formerly non-pathogenic mutants are no longer restricted in growth. Thus pathogenic success occurred by fungal control of plant cell death, when autophagy was inhibited. Oppositely, TYLCV pathogen induces plant autophagy at the early stages of infection, while later on activation of autophagy was not observed (Gorovits et al. 2016). Hence, we propose that TYLCV-induced autophagy counteracts *S. sclerotiorum* inhibition of autophagy in simultaneously infected tomatoes, and this encounter is the base of the temporary suppression of fungal pathogenicity. *B. cinerea* does not overcome the *S. sclerotiorum* biotrophic phase, there is no down-regulation of autophagy, and TYLCV does not induce the suppression of *B. cinerea* stress.

Conclusions

The demand for plant crops on the one hand and climate changes on the other request the development of cultivars with multi-stress resistances, a feat that cannot be obtained by pyramiding single stress resistance traits. We proposed an original approach suggesting exploiting the deleterious effects of viruses to protect plants from other stresses. One component the dual relationship is based on the paradigm stating that the severe tomato pathogen TYLCV suppresses pathogen-induced cell death to favorite its replication and spread. The other component states that by doing so, TYLCV also suppresses the plant response to several other stresses. In this way, TYLCV prevents plant death, allows its host to grow and develop under extreme environmental conditions. Therefore, TYLCV pre-inoculation of TYLCV-resistant tomatoes can be cultivated in regions with hot climate. It might be possible to use symptomless TYLCV mutants to pre-inoculate susceptible cultivars with the same effects.

Abbreviations

HR: Hypersensitive response; HSF: Heat stress transcription factor; HSP: Heat stress protein; ROS: Reactive oxygen species; TYLCV: *Tomato yellow leaf curl virus*

Acknowledgements
Not applicable.

Authors' contributions
GR initiated the concept. The experiments were supervised by GR and CH in Israel, and by AG in Jordan. SI and AM conducted the research in Israel and Jordan, respectively, together with the other authors. The manuscript was written by GR, CH, and AG. All authors read and approved the final manuscript.

Funding
This research was supported by a grant from the U.S. Agency for International Development, Middle East Research and Cooperation (MERC) program (M36–015).

Availability of data and materials
Not applicable.

Ethic approval and consent to participate
The research described in the manuscript does not involve human subject. We used commercial varieties of plants (tomato) as well as lines obtained by classical breeding (not GMOs). The authors also confirm that there are no disputes over the ownership of the data presented in the paper.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 14 January 2019 Accepted: 17 May 2019
Published online: 27 May 2019

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