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TRPV1 antagonists may exacerbate sepsis in aged mice: Should we be nervous?

Comment on: Wanner SP, et al. Cell Cycle 2012; 11:343–9; PMID:22214765; http://dx.doi.org/10.4161/cc.11.2.18772

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Desensitization of nociceptive neurons to capsaicin has a clear analgesic potential. Indeed, a high concentration capsaicin patch is already in clinical use to relieve neuropathic pain. The cloning of the capsaicin receptor TRPV1 has spurred considerable efforts in the pharmaceutical industry to find potent, small-molecule TRPV1 antagonists.[1] However, adverse effects have so far prevented any TRPV1 antagonists from advancing beyond phase II trials. In particular, concerns have surfaced around the effects of antagonizing TRPV1 on thermoregulation (hyperthermia) and on the ability to detect noxious heat (risk for scalding injury).[1] In a previous issue, Romanovsky and coworkers raised the possibility that TRPV1 blockade might also affect the response to sepsis, especially in older hosts.[2]

This is concerning, because both systemic inflammatory response syndrome (SIRS), which can occur following tissue damage, and sepsis, which occurs with microbial infection, are major public health problems and cause thousands of deaths every year.[3,4] In addition, despite extensive research into the inflammatory cascade triggered during SIRS and sepsis, the field has witnessed many failed clinical trials with drugs that alter the inflammatory response.[3] That some anti-inflammatory drugs lacked beneficial effects while others were harmful attests to the complexity and to the potential hazard of perturbing the inflammatory response.

Researchers have shown that the inflammatory response is modulated by a number of humoral and neural processes. Among the neural processes, the cholinergic anti-inflammatory pathway is long recognized.[5] More recently, TRPV1-expressing sensory neurons have emerged as potential players in modulating the inflammatory response during SIRS and sepsis. But how can TRPV1-expressing neurons play a role in inflammation? These neurons are known to release neuropeptides (e.g., substance P and calcitonin gene-related peptide) that initiate the cascade of neurogenic inflammation.[1] Indeed, TRPV1 blockade decreases neurogenic inflammation.[6]

Recent studies demonstrate that during LPS-induced SIRS in mice, TRPV1 deficiency is associated with increased inflammatory mediators and exacerbated organ damage.[7] Moreover, pharmacological TRPV1 blockade decreases survival.[8] However, the effect of TRPV1 actually varies depending on the insult (sepsis or LPS) and the mode of receptor blockade (desensitization, antagonism or gene disruption). In mice, both genetic deletion of TRPV1 and its desensitization to the ultrapotent agonist resiniferatoxin worsen survival and decrease bacterial clearance during polymicrobial sepsis but were without significant effect when LPS (without infection) triggered the inflammatory response.[8]

Studies with the relatively non-selective TRPV1 antagonist, capsazepine, yielded conflicting results. In mice with LPS-induced SIRS, capsazepine worsened survival.[8] By contrast, when administered before the onset of infection and sepsis, capsazepine actually improved survival.[9] Clearly, the role of TRPV1-expressing sensory neurons in SIRS and sepsis is incompletely understood, and the net effect of TRPV1 disruption seems to vary depending on the insult and the mode of disruption.

An underrecognized factor in TRPV1 actions is aging. For example, compared with their wild-type littermates, *Trpv1*-knockout mice are leaner when they are young but are more obese when they are getting old.[1]

Using a potent and selective TRPV1 antagonist, AMG517, Romanovsky suggests that aging may also alter the role of TRPV1 in LPS-induced SIRS.[2] While some might question the statistical power of some experiments, they confirm previous findings with capsazepine in young animals that TRPV1 antagonism worsens survival after LPS challenge. Surprisingly, this effect is reversed in older mice where AMG517 improves survival. These findings suggest that during LPS-induced SIRS, the role of TRPV1 might reverse with aging from anti-inflammatory to pro-inflammatory. Conversely, in the setting of infection, older TRPV1-deficient animals die earlier than controls, similar to findings previously reported in younger septic mice.[8]

In conclusion, aging seems to reverse the role of TRPV1 from anti-inflammatory to pro-inflammatory during SIRS but not sepsis. This is supported by the decreased serum levels of tumor necrosis factor, a known pro-inflammatory mediator, in LPS-challenged *Trpv1*-knockout older mice.[2] While it is tempting to categorize TRPV1 as anti-inflammatory vs. pro-inflammatory, one might argue that the inflammatory response in SIRS and sepsis is complex, and the presented data are far from being conclusive. Despite these issues, this is an important contribution to our understanding

of the role of TRPV1 in inflammatory response. Indeed, since TRPV1 blockade has been used clinically,[1] there is a real need to investigate the mechanisms involved more deeply. Should we be nervous? At a minimum, we should be vigilant.

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TRIM8 and p53: Making the right decision

Comment on: Caratozzolo MF, et al. Cell Cycle 2012; 11:511–23; PMID: 22262183; http://dx.doi.org/10.4161/cc.11.3.19008

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http://dx.doi.org/10.4161/cc.11.4.19359

Despite the growing number of functions assigned, ranging from pigmentation to fertility, the main role of the tumor suppressor protein p53 remains to preserve genome integrity by controlling two key biological outcomes of genome perturbation: the induction of cell cycle arrest, allowing DNA repair or, when the damage is irreparable, the induction of programmed cell death.[1] The choice between cell cycle arrest and apoptosis is influenced by different p53-dependent transcriptional programs that either involve cyclin-dependent kinase inhibitors (such as p21/WAF1) or apoptotic genes, such as p53AIP1, NOXA and Bax.[2]

How the decision is made at the molecular level is still the focus of intense research efforts, but it is clear that p53 post-translational modifications are key determinants of this decision: p53 phosphorylation on Ser-15 and Ser-20 residues is associated with cell cycle arrest, while Ser-46 phosphorylation is linked to cell death.[3] Protein acetylation at defined residues was also associated to the activation of apoptotic genes by p53. More recently, p53 ubiquitination, was found to affect, under certain conditions, the activity of p53 rather than stability. Ubiquitinated p53 was found in complexes bound to cell cycle arrest but not apoptosis genes, suggesting that p53 ubiquitination contributes to the selection of its transcriptional targets.[4] p53 ubiquitination is influenced by a plethora of ubiquitin ligases, most of them characterized for their ability to flag p53 for proteasome-mediated degradation.[5]

Among these, recent studies have indicated that some members of the tripartite motif (TRIM) proteins (one of the subfamilies of the RING type E3 ubiquitin ligases), which function as important regulators for carcinogenesis, are downregulated in tumors and act as important p53 regulators.[6] The RING domain of TRIM24 functions as an E3-ubiquitin ligase that targets p53 for degradation, and its depletion induces p53-dependent apoptosis.[7] The promyelocytic leukemia protein PML/TRIM19 is a p53 target that facilitates p53-Thr18 phosphorylation in response to DNA damage by recruiting p53 into PML nuclear bodies, thereby leading to p53 activation by protecting it from MDM2 inhibition. More recently, the ataxia telangiectasia group D-complementing ATDC/TRIM29 protein has been shown to bind and antagonize p53-mediated functions.[6]

In a very interesting article appeared in a previous issue of *Cell Cycle*, Caratozzolo and colleagues[8] identified in the E3 ubiquitin ligase TRIM8 as a key regulator of p53 in the cell cycle arrest vs. apoptosis decision. They showed that p53 directly activates TRIM8 transcription after DNA damage through a p53-responsive element in the first intron of TRIM8 gene. Once upregulated by p53, TRIM8 directly interacts with p53, inducing its stabilization by inhibiting MDM2 binding and, most interestingly, activating the cell cycle arrest transcriptional program but not apoptosis. This is accompanied by an increase of Ser-15 and Ser-20 phosphorylated p53 level but not of Ser-46, and, indeed, selective TRIM8 depletion facilitates DNA damage-induced apoptosis. Exogenous TRIM8 expression induced cell cycle arrest only in cell lines harboring wild-type p53 and had no effect in p53-null cells, indicating that TRIM8-induced cell cycle arrest is p53-dependent.

These findings highlight the importance of a novel feedback loop regulating the p53-dependent transcriptional program activated by DNA damage. Naturally, the findings of Caratozzolo et al. also generate questions. How does TRIM8 affect p53 ubiquitination? How are TRIM8 binding and p53 phosphorylation interconnected? Which comes first? Does TRIM8 also affect p53 acetylation? Are the other p53 family members involved in this feedback loop?

Future studies will certainly help address some of these questions and enhance our understanding of p53-related network, the ultimate beneficiaries being cancer-afflicted patients and their families.

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