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# INTERSPECIES CHEMICAL SIGNALS RELEASED INTO THE ENVIRONMENT MAY CREATE XENOHORMETIC, HORMETIC AND CYTOSTATIC SELECTIVE FORCES THAT DRIVE THE ECOSYSTEMIC EVOLUTION OF LONGEVITY REGULATION MECHANISMS

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□ Various organisms (*i.e.*, bacteria, fungi, plants and animals) within an ecosystem can synthesize and release into the environment certain longevity-extending small molecules. Here we hypothesize that these interspecies chemical signals can create xenohormetic, hormetic and cytostatic selective forces driving the ecosystemic evolution of longevity regulation mechanisms. In our hypothesis, following their release into the environment by one species of the organisms composing an ecosystem, such small molecules can activate anti-aging processes and/or inhibit pro-aging processes in other species within the ecosystem. The organisms that possess the most effective (as compared to their counterparts of the same species) mechanisms for sensing the chemical signals produced and released by other species and for responding to such signals by undergoing certain hormetic and/or cytostatic life-extending changes to their metabolism and physiology are expected to live longer then their counterparts within the ecosystem. Thus, the ability of a species of the organisms composing an ecosystem to undergo life-extending metabolic or physiological changes in response to hormetic or cytostatic chemical compounds released to the ecosystem by other species: 1) increases its chances of survival; 2) creates selective forces aimed at maintaining such ability; and 3) enables the evolution of longevity regulation mechanisms.

*Key words: Longevity, evolution, hormesis, phytochemicals, rapamycin, bile acids*

## INTRODUCTION

Aging of multicellular and unicellular eukaryotic organisms is a highly complex biological phenomenon, which affects numerous processes within cells (Guarente *et al.* 2008; Fontana *et al.* 2010; Partridge 2010; Masoro and Austad 2011). These cellular processes include cell cycle, cell growth, stress response, protein folding, apoptosis, autophagy, proteasomal protein degradation, actin organization, signal transduction, nuclear DNA replication, chromatin assembly and maintenance, ribosome biogenesis and translation, lipid and carbohydrate metabolism, oxidative metabolism in mitochondria, $NAD^+$ homeostasis, amino acid biosynthesis

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and degradation, and ammonium and amino acid uptake (Greer and Brunet 2008; Lin and Sinclair 2008; Narasimhan *et al.* 2009; Kaeberlein 2010; Dillin and Cohen 2011). Across phyla, such plethora of longevity-defining processes is governed by a nutrient signaling network integrating the AMP-activated protein kinase/target of rapamycin (AMPK/TOR), cAMP/protein kinase A (cAMP/PKA) and insulin/insulin-like growth factor 1 (IGF-1) pathways, as well as a sirtuin-governed protein deacetylation module (Yan *et al.* 2007; Greer and Brunet 2008; Finkel *et al.* 2009; Narasimhan *et al.* 2009; Fontana *et al.* 2010; Kenyon 2010). Because this evolutionarily conserved signaling network regulates longevity only in response to certain changes in the organismal and intracellular nutrient and energy status, it is "adaptable" by its nature (Goldberg *et al.* 2010). By altering the organismal and intracellular nutrient and energy status, caloric restriction and dietary restriction extend longevity and improve health across species by modulating the adaptable longevity network (Weindruch and Walford 1988; Masoro 2002; Sinclair 2005; Mair and Dillin 2008; Colman *et al.* 2009; Fontana *et al.* 2010). Unlike signaling pathways and sirtuin-governed protein deacetylation module integrated into the adaptable longevity network, some longevity-defining pathways are "constitutive" or "housekeeping" by their nature as they regulate longevity irrespective of the organismal and intracellular nutrient status (Goldberg *et al.* 2010).

It should be stressed that both adaptable and housekeeping longevity pathways are the targets of longevity-extending and health-improving small molecules that are produced and then released into the environment by various organisms (*i.e.*, bacteria, fungi, plants and animals) within an ecosystem. We therefore propose a hypothesis in which interspecies chemical signals released into the environment create xenohormetic, hormetic and cytostatic selective forces that empower the ecosystemic evolution of longevity regulation mechanisms.

## PLANTS AND OTHER AUTOTROPHS RELEASE INTO THE ENVIRONMENT XENOHORMETIC AND CYTOSTATIC INTERSPECIES CHEMICAL SIGNALS THAT EXTEND LONGEVITY OF OTHER ORGANISMS WITHIN AN ECOSYSTEM

According to the "xenohormesis" hypothesis of Howitz and Sinclair, in response to various hormetic environmental stresses - such as UV light, dehydration, infection, predation, cellular damage and nutrient deprivation - plants and other autotrophic organisms synthesize a group of secondary metabolites called xenohormetic phytochemicals (Howitz *et al.* 2003; Lamming *et al.* 2004; Howitz and Sinclair 2008). Prior to being released into the environment, these secondary metabolites activate defense systems protecting the host autotrophic organisms against hormetic environmental stresses that caused their synthesis (Lamming *et*

*al.* 2004; Howitz and Sinclair 2008). After being released into the environment, these xenohormetic phytochemicals provide benefits to health and longevity of heterotrophic organisms within the ecosystem. It was proposed that xenohormetic phytochemicals cause such life-extending and health-improving effects not by operating as mildly toxic hormetic molecules, but by activating the key enzymes of stress-response, anti-aging pathways known to govern longevity-related processes in heterotrophic organisms (Howitz *et al.* 2003; Lamming *et al.* 2004; Howitz and Sinclair 2008). Recent studies revealed that some xenohormetic phytochemicals, such as resveratrol and caffeine, extend longevity of heterotrophic organisms by attenuating the adaptable TOR signaling pathway known to accelerate their aging (Dasgupta and Milbrandt 2007; Wanke *et al.* 2008; Armour *et al.* 2009; Blagosklonny 2009; Demidenko and Blagosklonny 2009). Because the TOR pathway also plays a pivotal role in promoting proliferative growth of all heterotrophic organisms, resveratrol and caffeine exhibit a cytostatic effect in these organisms (Blagosklonny 2009; Blagosklonny and Hall 2009; Demidenko and Blagosklonny 2009; Blagosklonny 2010).

By extending the xenohormesis hypothesis of Howitz and Sinclair, we propose that within each of the heterotrophic species composing an ecosystem there are organisms that 1) possess the most effective (as compared to their counterparts of the same species) mechanisms for sensing xenohormetic and cytostatic phytochemicals released into the environment by autotrophic species; and 2) can respond to these phytochemicals by activating the key enzymes of stress-response, anti-aging pathways and/or by attenuating the adaptable, pro-aging TOR signaling pathway - thereby undergoing life-extending changes to their metabolism and physiology. These heterotrophic organisms are expected to live longer then their counterparts within the same species. Thus, their ability to sense the longevity-extending xenohormetic and cytostatic phytochemicals released into the environment by autotrophic species and to respond to these phytochemicals by undergoing certain life-extending metabolic and physiological changes will: 1) increase their chances of survival; 2) create selective forces aimed at maintaining such ability; and 3) power the evolution of their longevity regulation mechanisms.

## MAMMALS RELEASE INTO THE ENVIRONMENT BILE ACIDS, HORMETIC INTERSPECIES CHEMICAL SIGNALS THAT EXTEND LONGEVITY OF YEAST AND PERHAPS OF OTHER ORGANISMS WITHIN AN ECOSYSTEM

In mammals, bile acids operate not only as trophic factors for the enteric epithelium and detergents for the emulsification and absorption of dietary lipids, but also as signaling molecules regulating lipid, glucose and energy homeostasis and activating detoxification of xenobiotics (Ramalho *et al.* 2008; Thomas *et al.* 2008; Amaral *et al.* 2009; Hylemon *et*

*al.* 2009; Lefebvre *et al.* 2009; Vallim and Edwards 2009). Bile acids have been shown to cause numerous health-improving metabolic effects in mammals and to protect them from xenobiotic toxins (Ramalho *et al.* 2008; Thomas *et al.* 2008; Amaral *et al.* 2009; Hylemon *et al.* 2009; Lefebvre *et al.* 2009; Vallim and Edwards 2009). Therefore, it was proposed that by promoting chemical hormesis in mammals, bile acids – mildly toxic molecules with detergent-like properties – may extend their longevity by acting as endobiotic regulators of aging (Amador-Noguez *et al.* 2004; Amador-Noguez *et al.* 2007; Gems, 2007; Gems and Partridge 2008).

Importantly, our recent study identified lithocholic acid, a bile acid, as an anti-aging compound that extends yeast longevity by activating a compendium of anti-aging processes and attenuating a distinct set of pro-aging processes (Goldberg *et al.* 2010). Unlike mammals, yeast do not synthesize bile acids (Lefebvre *et al.*, 2009; Monte *et al.*, 2009; Goldberg *et al.* 2010). We therefore propose that bile acids released into the environment by mammals may act as interspecies chemical signals extending longevity of yeast species and, perhaps, of other organisms that can: 1) sense these mildly toxic molecules with detergent-like properties; and 2) respond to the resulting mild cellular damage by developing the most efficient stress protective mechanisms. We hypothesize that such mechanisms may provide effective protection of yeast and other organisms not only against cellular damage caused by bile acids but also against molecular and cellular damage accumulated with age. Thus, those species of the organisms within an ecosystem that that have been selected for the most effective (as compared to their counterparts of the same species) mechanisms providing protection against bile acids are expected to 1) live longer then their counterparts within the same species; and 2) evolve the most effective anti-aging mechanisms that are sensitive to regulation by bile acids. Thus, the ability of certain non-mammalian species within an ecosystem to sense bile acids produced by mammals and then to respond by undergoing certain longevity-extending changes to their physiology will increase their chances of survival - thereby creating selective force aimed at maintaining such ability and driving the evolution of their longevity regulation mechanisms.

## SOIL BACTERIA RELEASE INTO THE ENVIRONMENT RAPAMYCIN, A CYTOSTATIC INTERSPECIES CHEMICAL SIGNAL THAT EXTENDS LONGEVITY OF OTHER ORGANISMS WITHIN AN ECOSYSTEM

The adaptable TOR signaling pathway can be attenuated not only by resveratrol and spermidine - the two longevity-extending xenohormetic and cytostatic phytochemicals released into the environment by autotrophic species – but also by rapamycin (Wullschleger *et al.* 2006; Blagosklonny and Hall 2009; Hands *et al.* 2009). Rapamycin - a macrocyclic lactone synthesized by soil bacteria to inhibit growth of fungal com-

petitors - extends longevity of yeast, fruit flies and mice by specifically inhibiting the nutrient-sensory protein kinase TOR, a master negative regulator of the pro-aging TOR signaling pathway (Powers *et al.* 2006; Blagosklonny and Hall 2009; Hands *et al.* 2009; Harrison *et al.* 2009; Bjedov et al. 2010).

Rapamycin exhibits a potent cytostatic effect by causing G1 cell cycle arrest and greatly delaying proliferative growth of organisms across phyla (Powers *et al.* 2006; Wullschleger *et al.* 2006; Blagosklonny and Hall 2009; Hands *et al.* 2009). We therefore hypothesize that rapamycin released into the environment by soil bacteria not only suppresses growth of fungal competitors, but also may create selective pressure for the evolution of yeast, fruit fly and mammalian species that can respond to rapamycin-induced growth retardation by developing certain mechanisms aimed at such remodeling of their anabolic and catabolic processes that would increase their chances of survival under conditions of slow growth. We propose that some of these mechanisms delay aging by optimizing essential longevity-related processes and remain sensitive to modulation by rapamycin. Therefore, the ability of yeast, fruit fly and mammalian species composing an ecosystem to undergo life-extending metabolic or physiological changes in response to rapamycin produced by soil bacteria will: 1) increase their chances of survival; 2) create selective forces aimed at maintaining such ability; and 3) empower the evolution of longevity regulation mechanisms.

## A HYPOTHESIS OF THE XENOHORMETIC, HORMETIC AND CYTOSTATIC SELECTIVE FORCES THAT PROPEL THE ECOSYSTEMIC EVOLUTION OF LONGEVITY REGULATION MECHANISMS

Our analysis of how several small molecules synthesized and released into the environment by one species of the organisms composing an ecosystem extend longevity of other species within this ecosystem suggests a hypothesis in which these interspecies chemical signals create xenohormetic, hormetic and cytostatic selective forces that impel the ecosystemic evolution of longevity regulation mechanisms. In our hypothesis, after being released into the environment by one species of organisms capable of synthesizing such small molecules, they can activate anti-aging processes and/or inhibit pro-aging processes in other species within an ecosystem. Within each of these other species, there are organisms that possess the most effective (as compared to their counterparts of the same species) mechanisms for sensing the interspecies chemical signals and for responding to such signals by undergoing certain life-extending changes to their metabolism and physiology; such life-extending changes could be hormetic and/or cytostatic by their nature. These organisms therefore are expected to live longer then their counterparts of the same species within the ecosystem. Thus, the ability of a species of the organisms com-

posing an ecosystem to sense the longevity-modulating interspecies chemical signals released into the environment by other species within the ecosystem and to respond to these signals by undergoing certain life-extending metabolic and physiological changes is expected to increase its chances to survive, thereby creating selective force aimed at maintaining such ability. Our hypothesis implies that the evolution of longevity regulation mechanisms in each species of the organisms composing an ecosystem is driven by the ability of this species to undergo specific life-extending metabolic or physiological changes in response to hormetic or cytostatic chemical compounds that are released to the ecosystem by other species.

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## CONFLICT OF INTEREST STATEMENT

The authors of this manuscript have no conflict of interest to declare.

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