

Do airborne biogenic chemicals interact with the PI3K/Akt/mTOR cell signalling pathway to benefit human health and wellbeing in rural and coastal environments?

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Abstract

Living and taking recreation in rural and coastal environments promote health and wellbeing, although the causal factors involved are unclear. It has been proposed that such environments provide a counter to the stresses of everyday living, leading to enhanced mental and physical health. Living in natural environments will result in airborne exposure to a wide range of biogenic chemicals through inhalation and ingestion of airborne microbiota and particles. The “biogenics” hypothesis formulated here is that regular exposure to low concentrations of mixtures of natural compounds and toxins in natural environments confers pleiotropic health benefits by inhibiting the activities of interconnected cell signalling systems, particularly PI3K/Akt/mTORC1. When overactive, Akt and mTOR (mTORC1) can lead to many pathological processes including cancers, diabetes, inflammation, immunosuppression, and neurodegenerative diseases. There is a substantial body of evidence that many natural products (i.e., from bacteria, algae, fungi and higher plants) inhibit the activities of these protein kinases. Other mTOR-related interconnected metabolic control “switches” (e.g., PTEN & NF-κB), autophagy and other cytoprotective processes are also affected by natural products.

The “biogenics” hypothesis formulated here is that regular intermittent exposure to a mixture of airborne biogenic compounds in natural environments confers pleiotropic health benefits by inhibiting activities of the highly interconnected PI3K/Akt/mTORC1 system. It is proposed that future experimental exposures to biogenic aerosols in animal models coupled with epidemiology, should target the activities of the various kinases in the PI3K/Akt/mTORC1 systems and related physiological

hesis.

Key words: *autophagy, cell-signalling, green-blue space, mTOR, phytochemicals.*

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1. INTRODUCTION

Epidemiological evidence to support positive health benefits (biophilia – “green-blue space” effect) from living in and taking recreation in natural environments is mounting (Aspinall et al., 2015; Berman et al., 2008; Dadvand et al., 2005; Depledge et al., 2013; Maas et al., 2006; Park et al., 2007, 2010; Rook, 2013; Sandifer et al., 2015; SarrafZadegan & AminiNik, 1997; Wheeler et al., 2012; White et al., 2010, 2013; Wilson, 1984). Beneficial effects in wellbeing are especially prominent in individuals of lower socio-economic status (Maas et al., 2009; Mitchell & Popham, 2008; Dadvand et al., 2012; Wheeler et al., 2012). The causative factors are unknown, although to date these beneficial effects have been attributed largely psychological mechanisms involving a reduction in stress through taking more exercise and living in aesthetically pleasing situations (White et al., 2014). However, psychological mechanisms are unlikely to explain the longer-lasting physiological health benefits, so other environmental factors may be involved, including low-level exposure to natural airborne microbiota and biogenic products (including phytochemical and particulate allergens) that are inhaled and ingested in rural and coastal areas (Christensen et al., 1999; Després et al., 2012; Jones & Harrison, 2003; Matthias-Maser et al., 2000; Matsunaga et al., 2011; Ong et al., 1986, 1994; Paré & Tumlinson, 1999; Postolache et al., 2007; Rook, 2013; Seedorf et al., 2014).

There is a growing body of evidence that inhalation and ingestion (i.e., via the upper respiratory tract mucus) of the airborne microbiota may be contributing to more effective immunoregulation (Cox et al., 2014; Rook, 2013; Seedorf et al., 2014; Smillie et al., 2011), while airborne biogenic chemicals are present in sufficient concentrations in aerosols, microbiota, spores and pollen to cause toxicity and allergic reactions (Artaxo & Hansson, 1995; Bahadur et al., 2010; Bennett & Klich, 2003; Christensen et al., 1999; D'amato, 2000; Gerssen et al., 2010; Graham et al., 2003; Lu et al., 2013; Dungan, 2011; Jones & Harrison, 2004; Krivácsy et al., 2008; Kroll & Seinfeld, 2008; Kulmala et al., 2001; Matthias-Maser et al., 2000; Paré & Tumlinson, 1999; Pierce & Henry, 2009; Rogge et al., 1993a, c; Russell et al., 2010; Skaug et al., 2001; Wang, 2008). Recently, Rook (2013) has presented a convincing argument that human exposure to microbiota and parasites (“old friends” hypothesis) contributes to improved immunoregulation and reduction in inflammation associated with many pathologies. This paper explores a complementary scenario to the psychological and immunoregulatory explanations, based on exposure to bioactive biogenic compounds that can be found in these natural environments. A testable conceptual model is developed for the potential mechanisms of action of such biogenic products and how these mechanisms may relate to the observed health and wellbeing benefits.

2. RATIONALE

The sources of airborne environmental biogenic products in aerosols are widespread (see review by Després et al., 2012; and references for Table 1). These include volatile plant products (e.g., terpenoids), polyphenols (so called “antioxidants”, e.g., anthocyanins, anthocyanidins, catechins, epicatechins, flavanols, flavanones, flavonoids, fulvic acids, humics, isoflavones, lignans,

1 proanthocyanidins, procyanidins, stilbenes, tannins, etc.), isothiocyanates, carotenoids, allyl sulfides,
2 pyrrolizidone alkaloids and other phytotoxins from plant and macroalgal fragments, pollen, lichen,
3 fungi (and spores), and fern spores; antibiotics, phytochemicals, phytotoxins and viral proteins from
4 airborne soil particle-associated viruses, bacteria, cyanobacteria, fungi and plant fragments; as well
5 as algal, bacterial and cyanobacterial toxins in sea-surface microlayer/seawater aerosols (see
6 references for Table 1; Bennick, 2002; Christensen et al., 1999; Cunliffe et al., 2013; Després et al.,
7 2012; Fleming et al., 2005, 2007; Halliwell, 2009; Matsunaga et al., 2011; O'Dowd & Leeuw, 2007;
8 Pierce, 1986; Postolache et al., 2007; Rook, 2013; van Strien et al., 2004).

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12 During the course of hominid evolution our ancestors will have been exposed to a legion of biogenic
13 products through inhalation/ingestion and as part of the diet (Abrahams, 2002; Bennick, 2002;
14 Christensen et al., 1999; Del Rio et al., 2013; Kennedy & Wightman, 2011; Lippmann et al., 1980;
15 Malloy & Marr, 1997; Matricardi et al., 2000; Postolache et al., 2007; Rook, 2013; Skaug et al., 2001).
16 Over the course of this longstanding exposure, adaptations will have occurred that facilitate tolerance
17 of these often toxic compounds (Christensen et al., 1999; Del Rio et al., 2013; Postolache et al.,
18 2007). Many of these compounds may actually facilitate human wellbeing; and removal of this
19 exposure as a result of the relatively recent (in evolutionary terms) massive movement of human
20 populations to urbanised environments may have contributed to a general decline in wellbeing. Could
21 it be that rural and coastal environments are the norm for our species, as our ancestors frequently
22 used coastal corridors for the global expansion of mankind (Del Rio et al., 2013; Rook, 2013)?

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30 Prominent among the biogenic phytochemical compounds of interest here are the so called
31 polyphenolic antioxidants (Pandey & Rizvi, 2009). These polyphenolic compounds are secondary
32 metabolites of plants: they are often toxic at high concentrations, and have a defensive role in plants
33 and plant pathology, where they act as natural pesticides against invading organisms (i.e., herbivores,
34 nematodes, phytophagous insects, and fungal and bacterial pathogens; Beckman, 2000, Bennick,
35 2002; Paré & Tumlinson, 1999). While most phytochemical uptake in humans is dietary from
36 vegetables and fruit (Bennick, 2002; Carluccio et al., 2003; Del Rio et al., 2013; Kennedy &
37 Wightman), there is a large gap in our knowledge concerning alternative or complementary exposure
38 routes for phytochemicals as discussed in this paper. Nonetheless, there is an extensive body of
39 literature on the supposed health benefits of the consumption of phytochemicals, particularly
40 polyphenolics (e.g., the "Mediterranean Diet"; Carluccio et al., 2003; Del Rio et al., 2013), with
41 considerable interest being shown in these types of compounds by the pharmaceutical industry.
42 Polyphenolics occur at a concentration around 2-3 mg/g in most fruits, such as grapes, apple, pear,
43 cherries and berries; and a glass of red wine (e.g., contains among many others, the polyphenolic
44 stilbenoid – resveratrol) or a cup of coffee, chocolate or tea will contain approximately 100mg of
45 polyphenols (Del Rio et al., 2013; Pandey & Rizvi, 2009). Dietary polyphenolics appear in the
46 circulatory system as metabolites of Phase II biotransformation, and their plasma concentration rarely
47 exceeds nM concentrations, indicating that they can be bioactive at very low levels (Del Rio et al.,
48 2013; Kennedy & Wightman, 2011). However, while the weight of evidence indicates that many
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1 ingested polyphenols are beneficial for health, some airborne polyphenols can be harmful such as
2 tannins causing byssinosis or “brown lung disease” (Bennick, 2002, Del Rio et al., 2013; Kennedy &
3 Wightman, 2011; Pandey & Rizvi, 2009).
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5 Volatile phytochemicals (volatile organic chemicals - VOCs) such as terpenoids have also been
6 implicated in beneficial roles in human health, with some having anti-cancer properties (Chen et al.,
7 2014; Kusuhabara et al., 2012; Matsunaga et al., 2011; Park et al., 2010b; Son et al., 2013). A number
8 of terpenoids inhibit NF- κ B signalling reducing inflammation and inhibit mTOR and activating
9 autophagy (Cock, 2013; Russo et al., 2014; Salminen et al., 2008). The Japanese practice of “Forest
10 Bathing” or Shinrin-yoku has been shown to have significant health benefits including a reduction in
11 cortisol, which can be a consequence of mTOR inhibition (De Martino et al., 2012; Park et al., 2007,
12 2010a). Taking recreation in forests, as in Shinrin-yoku, will result in exposure to airborne VOCs
13 including compounds such as α -pinene, β -pinene, d-limonene, camphene, and α -terpinene, all of
14 which can have health benefits (Cock, 2013; Russo et al., 2014; Son et al., 2013).
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21 Many of the biogenic compounds that will be discussed in this paper are toxic at higher
22 concentrations, although generally the concentrations encountered from airborne sources will be
23 significantly below the toxic threshold (Després et al., 2012). This raises the issue of whether any
24 physiological responses reactions to these compounds will constitute a hormetic effect (Afanas’ev,
25 2010; Blagosklonny, 2011; Duke, 2011; Hooper et al., 2010; Menendez et al., 2013). Hormesis is
26 discussed in a later section, and refers to a biphasic dose response to an environmental agent
27 characterized by low dose stimulation or beneficial effect and a high dose inhibitory or toxic effect
28 (Mattson, 2008).
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34 The hypothesis developed here is that airborne biogenic compounds in rural and coastal
35 environments interact with specific cell signalling pathways to exert beneficial effects that parallel the
36 effects of caloric restriction (CR), by targeting the PI3K/AktT/mTORC1 (PI3K - phosphatidylinositol-3
37 kinase, Akt - serine/threonine kinase or protein kinase B - PKB, and mTORC1 - mechanis c target of
38 rapamycin complex 1), NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) and
39 PTEN (phosphatase and tensin homolog, tumour suppressor) pathways and autophagy (Fig. 1; for a
40 detailed schematic of mTOR-linked cell signalling pathways – see the review by Laplante & Sabatini,
41 2009; Zhang et al., 2012). Inhibition of these pathways, with the exception of PTEN can result in anti-
42 inflammatory, cardiovascular, anti-diabetes, neurological, anti-psychotic and anti-cancer health
43 benefits (Afanas’ev, 2010; Arafa et al., 2011; Asnaghi et al., 2010; Balistreri et al., 2013; Ballou & Lin,
44 2008; Bassères & Baldwin, 2006; Beevers et al., 2013; Blagosklonny, 2011; Corradetti & Guan, 2006;
45 Dan et al., 2008; de Souza et al., 2010; Deeb et al., 2007; Harries et al., 2012; Hau et al., 2013;
46 Johnson et al., 2009; Lamming et al., 2013; Laplante & Sabatini, 2010, 2012, 2013; Lee et al., 2013;
47 Madrid et al., 2001; Markman et al., 2010; Martin et al., 2012; Sabatini, 2006; Salminen &
48 Kaarniranta, 2009a, c; Steelman et al., 2011; Tan et al., 2014; Trocoli & Djavaheri-Mergny, 2011; von
49 Roemeling et al., 2013; Wang et al., 2009; Weijenberg et al., 2013; Xie et al., 2013; Zhang et al.,
50 2012; Zhang et al., 2011; Zhou et al., 2010).
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2 **3. INHALATION AND INGESTION OF NATURAL PRODUCTS**
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5 **3.1. Biogenic products in the natural environment**
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7 The air that we breath contains a plethora of particles including viruses, microbes, fungi, soil and plant
8 materials that will associate with the mucus membranes in our upper respiratory system and be
9 ingested (see Table 1 references and Abrahams, 2002; Després et al., 2012; Jones & Harrison, 2003;
10 Lippmann et al., 1980; Rook, 2014; Tsunetsugu et al., 2010; Williams, 1963; Womiloju et al., 2003).
11 The diversity of this exposure is much greater in the natural environment than in the urban built
12 environment (Fischer & Dott, 2003; Frohlich-Nowoisky 2009; Frumkin, 2001; Malloy & Marr, 1997;
13 Matricardi et al., 2000; Okuda et al., 2005; Rook, 2013; Womiloju, 2014).
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19 Bacteria, cyanobacteria, unicellular algae and macroalgae, plants and fungi all produce a wide variety
20 of biogenic products, many of which interact with biological systems (see Table 1). These include
21 antibiotics, microcystins, nodularins, polyphenols, algal toxins, mycotoxins, alkaloids and volatile
22 products, many of which can readily become airborne (Table 1). Some of these products are present
23 in airborne plant and macroalgal fragments, spores (bacteria, fungi and ferns), pollen grains and
24 associated with airborne soil particles. In coastal environments airborne nano- and micro-droplets of
25 seawater can carry algal, macroalgal (in fragments), cyanobacterial and bacterial products inland for
26 considerable distances (Table 1; Clarke & Zika, 2000; Cunliffe et al., 2013; Després et al., 2012;
27 Fleming et al., 2005, 2007; O'Dowd & Leeuw, 2007; Pierce, 1986; Pierce & Henry, 2008; Wang,
28 2008).
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36 **3.2. Biogenic and anthropogenic products in the built environment**
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38 The diversity and types of microbiota and fungi in the built environment is very different from the
39 natural environment, and is dominated by micrococcus species (Rook, 2013; Shelton et al., 2002).
40 Consequently, human exposure to the airborne microbes, spores and biogenic products in the built
41 environment will be likewise dissimilar to those in the natural environment. Built environments also
42 contain many synthetic and airborne combustion products (Pott & Stobert, 1983). The synthetic
43 contaminants will be derived from the treatment of building materials with biocides and various
44 surface treatments and fire retardents in soft furnishings and carpets (Reemtsma et al., 2008).
45 Combustion products will include polycyclic aromatic hydrocarbons, and nitrogen, oxygen and sulphur
46 heterocyclics derived from a range of industrial and domestic combustion processes, as well as
47 airborne urban road-tyre dust (Pott & Stobert, 1983; Rogge et al., 1993a, c).
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57 **4. CELLULAR TARGETS FOR BIOGENIC PRODUCTS**
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1 As indicated in the preceding section, humans are subjected to a highly diverse array of natural
2 products derived from the microbiota, fungi and plants; and also, man-made (anthropogenic) chemical
3 contaminants particularly in the urban environment (Table 1; Pott F, Stobert, 1983; Rogge et al.,
4 1993a, b). There is a huge scientific literature on the interactive and harmful effects of airborne
5 pollutants but rather less on the interactions and health effects of naturally occurring biogenic
6 products (Brunekreef & Forsberg, 2005; Del Rio et al., 2013; Rogge et al., 1993a, c).

7 8 9 **4.1. Interactions with cell signalling pathways (Fig. 1)**

10 11 **4.1.1. PI3K–Akt–mTOR**

12 Surprisingly, many of the airborne biogenic products that have been identified in the natural
13 environment interact with some of the key components of the cell signalling network in humans and all
14 other eukaryotic organisms (Fig. 1; Table 1). These components include the functional molecules of
15 the phosphatidylinositol 3'-kinase–Akt–mammalian target of rapamycin (PI3K–Akt–mTOR) pathway
16 (Fig. 1), which is strongly implicated in the control of cellular growth (see overviews by Afanas'ev,
17 2010; Asnaghi et al., 2010; Corradetti & Guan, 2006; Farrand et al., 2014; Laplante & Sabatini, 2012;
18 Markman et al., 2010; Martin et al., 2012). This pathway is strongly linked to regulation of growth,
19 protein synthesis, autophagy, cortisol concentration, innate immunity, inflammation,
20 neurodegeneration, T cell regulation (Treg), and the growth of many cancers, as well as the inhibition
21 of uptake of iodine (De Martino et al., 2012; de Souza et al., 2010; Gerriets & Rathmell, 2012).

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31 The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that controls many aspects
32 of cellular physiology, including transcription, translation, cell size, cytoskeletal organization and
33 autophagy (see reviews by Laplante & Sabatini, 2009, 2012). Recent advances in the mTOR
34 signalling field have found that mTOR exists in two heteromeric complexes, mTORC1 and mTORC2.
35 The activity of mTORC1 is regulated by the integration of many signals, including growth factors,
36 insulin, nutrients, exercise, energy availability, vitamin D and cellular stressors such as hypoxia,
37 osmotic stress, reactive oxygen species (ROS) and viral infection (Dreyer et al., 2006; Laplante &
38 Sabatini, 2009, 2012; Lisse & Hewison, 2011; Martin et al., 2012). Recent advances in the mTOR
39 signalling field have clarified how the two mTOR complexes are regulated (Laplante & Sabatini,
40 2009).

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47 The **PI3K/Akt/mTORC1 pathway** is an intracellular signalling pathway important in regulating cell
48 growth, apoptosis (Type 1 programmed cell death) and longevity, which when overactive can lead to
49 many pathological processes including cancers, diabetes, inflammation, immunosuppression, and
50 neurodegenerative diseases (Fig. 1; Laplante & Sabatini, 2012). PI3K activation in turn activates Akt,
51 which activates mTOR, and in many cancers, this pathway is overactive, thus reducing apoptosis and
52 allowing proliferation of abnormal cells (Dan et al., 2008; Laplante & Sabatini, 2009, 2012).
53 Consequently, some experimental cancer drugs aim to inhibit the signalling sequence at some point
54 (e.g., metformin and Torisel; von Roemeling et al., 2013). The PI3K pathway may also be overactive
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1 because PTEN (tumour suppressor) is faulty or deficient (Corradetti & Guan, 2006; Steelman et al.,
2 2011).

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4 mTOR (mTORC1) is also a nutrient and stress sensor and when active suppresses the process of
5 lysosomal autophagy which is crucial for the effective turnover of cellular proteins and organelles (Fig.
6 1; Laplante & Sabatini, 2012). Low nutrient levels and other environmental stressors (e.g., hypoxia,
7 excise), including many phytochemicals, switch mTORC1 off, hence activating autophagy (Cuervo,
8 2004; Kim et al., 2012; Levine & Kroemer, 2008, Klionsky et al., 2007; Moore et al., 2007; Nacarelli et
9 al., 2014; Zhang et al., 2012). Autophagy is important in removing oxidatively damaged and defective
10 proteins and organelles, and is strongly linked with longevity and protection against tumours (Cuervo,
11 2004; Kim et al., 2012; Levine & Kroemer, 2008; Martins et al., 2011; Moore, 2008; Moore et al.,
12 2008; Rubinsztein et al., 2011; Salminen & Kaarniranta, 2009a; Zhang et al., 2012).

13 14 15 16 17 18 19 4.1.2. *PTEN and NF- κ B*

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21 PTEN is a tumor suppressor protein, which is mediated via its phosphatase action. This phosphatase
22 acts as part of a chemical pathway that signals cells to stop dividing and can cause cells to undergo
23 Type 1 programmed cell death (apoptosis) when necessary. These functions prevent uncontrolled cell
24 growth that can lead to the formation of tumors (Fig. 1; Steelman et al., 2011). The polyphenol
25 resveratrol induces the expression of antioxidant enzymes such as catalase (Cat) and manganese
26 superoxide dismutase (MnSOD), at nutritionally relevant concentrations, through a mechanism
27 involving the PTEN/Akt signaling pathway (Inglés et al., 2014). Conversely, NF- κ B is considered to
28 play key roles in the development and progression of many cancers, the mechanisms whereby this
29 transcription factor is activated in cancer are poorly understood (Fig. 1; Balistreri et al., 2013;
30 Bassères & Baldwin, 2006; Madrid et al., 2001; Salminen & Kaarniranta, 2009b, 2010; Trocoli &
31 Djavaheri-Mergny, 2011; Wang et al., 2009). The serine–threonine kinase Akt is also a key
32 oncoprotein in a variety of cancers, which can be activated by mutations in PI3K, loss of
33 expression/activity of PTEN, or through signalling induced by growth factors and their receptors (Arafa
34 et al., 2011). A key effector of Akt-induced signaling is the regulatory protein mTOR (see above).
35 mTOR downstream from Akt controls NF- κ B activity in PTEN-null/inactive cancer cells via interaction
36 with IKK (inhibitor of nuclear factor kappa-B kinase), and stimulation and regulation of autophagy in
37 the context of ageing processes (Dan et al., 2008; Rubinsztein et al., 2011; Salminen et al., 2012).

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48 Given the key anti-apoptotic functions ascribed to NF- κ B (see Bassères & Baldwin 2006), it is likely
49 that NF- κ B activation downstream from Akt functions to promote cell survival. Previous evidence for
50 this was provided by Madrid et al. (2001). This may indicate that Akt, at least in the setting of loss of
51 PTEN function, promotes IKK-dependent activation of NF- κ B via mTOR and Raptor, which controls
52 the expression of certain key anti-apoptotic genes. In this pathway, TORC1 would promote cell
53 survival through a mechanism that is independent of the traditional translational-dependent pathways
54 associated with mTOR activity (Dan et al., 2008).

4.2. Autophagy, anti-ageing & possible hormetic-type effects

Inhibition of mTOR activates autophagy: a cellular physiological mechanism for cellular repair (cytoprotection) through the removal of damaged proteins, protein aggregates (e.g., in neurodegenerative diseases) and damaged or redundant organelles such as mitochondria (Fig. 2; Cuervo, 2004; Eskelinen et al., 2009; Mizushima et al., 2008). Consequently, the autophagic processes have been increasingly shown to have protective functions against ageing and many diseases including cancers, neurodegenerative diseases (Fig. 2; Cuervo, 2004; Ferrari et al., 2011; Hippert et al., 2006; Mizushima et al., 2008; Ozkan et al., 2015; Rubinsztein et al., 2011; Salminen & Kaarniranta, 2009a; Selvakumaran et al., 2013; Trocoli & Djavaheri-Mergny, 2011; Zhang et al., 2012). Autophagic lysosomal digestion is triggered by many environmental stressors including caloric restriction (CR), hypoxia, ROS, exercise, many toxins and phytochemicals, and sunlight and vitamin D mediated via the vitamin D receptor - VDR (Chatterjee et al., 2014; Delmas et al., 2011; Ferrari et al., 2011; Mestre & Columbo, 2013; Moore et al., 2008; Wu & Sun, 2011; Zhang et al., 2012).

Autophagy, triggered by inhibition of mTOR and other mTOR-independent pathways (e.g., SIRT 1 and VDR), is probably an important component of hormetic responses, particularly in anti-ageing processes (Blagosklonny, 2011, Kim et al., 2012; Martins et al., 2011; Moore & Stebbing, 1976; Rubinsztein et al., 2011; Salminen et al., 2012; Wu & Sun, 2011). mTOR (mTORC1) is also a nutrient and stress sensor that regulates lysosomal autophagy, apoptosis (Type 1 programmed cell death – PCD 1) and senescence, that when inhibited can have beneficial consequences as indicated above. In essence, many of the natural biogenic compounds described in this paper may act as caloric restriction (CR) mimetics: CR is well known to have beneficial effects in a wide range of organisms by increasing lifespan and reducing the risk from age-related cancers, cardiovascular and neurodegenerative diseases (Mattson & Wan, 2005; Fontana et al., 2010).

Cells use autophagy and the ubiquitin–proteasome system as their major protein degradation pathways (Cuervo, 2004; Klionsky et al., 2007; Kraft et al., 2010; Lamb et al., 2013). While the ubiquitin–proteasome system is involved in the rapid degradation of proteins, autophagy pathways can selectively remove protein aggregates and damaged or excess organelles. Although autophagy has long been viewed as a fairly random cytoplasmic degradation system, the involvement of ubiquitin as a specificity factor for selective autophagy is rapidly emerging (Kraft et al., 2010). Recent evidence also suggests strong interactions (crosstalk) between proteasome-mediated degradation and selective autophagy (Kraft et al., 2010).

Low-dose exposures to some phytochemicals can trigger a cellular stress response and subsequently induce adaptive stress resistance known as hormesis (Blagosklonny, 2011; Duke, 2011; Martins et al., 2011; Mattson, 2008). Stress resistance involves a number of molecular adaptations including activation of AMP kinase, autophagy, and alterations cell survival and longevity genes (Fig. 2). Salminen and Kaarniranta (2010) have proposed that anti-inflammatory and anti-cancer responses induced by phytochemicals are caused by phytohormetic stress resistance involving the suppression

1 of NF- κ B. The NF- κ B system is a pleiotropic regulator that has opposing effects, both detrimental and
2 beneficial (biphasic) responses (Salminen & Kaarniranta, 2010; Trocoli & Djavaheri-Mergny, 2011).
3 Its major function is maintaining innate immunity and protection against apoptosis as a result of tissue
4 damage. Autophagy is involved in several cellular functions regulated by NF- κ B including cell survival,
5 differentiation, senescence, inflammation, and immunity. On a molecular level, autophagy and NF- κ B
6 share common upstream signals and regulators and can control each other through positive or
7 negative feedback loops, thus ensuring homeostatic responses.
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11 If the hypothesis developed in this paper receives future support from epidemiological data, and
12 airborne biogenic agents are targeting key components of cell signalling such as mTOR, then any
13 accruing health benefits are like to involve cytoprotective processes such as autophagy in
14 counteracting cellular processes leading to disease and ageing. Exposure to sunlight (UV radiation)
15 and generation of vitamin D in rural and coastal populations in comparison to urban populations is
16 also likely to contribute to beneficial enhanced autophagy (Lisse & Hewison, 2012; Wu & Sun, 2011).
17 Extending this argument further: we can speculate that we would expect to see a reduction in vitamin
18 D induced autophagy in more northerly latitudes (Northern Hemisphere) with a corresponding
19 reduction in human health as has been observed (see review by Pearce & Cheetham, 2010).
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26 **4.3. Viruses and viral fragments**

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29 Viruses and viral fragments will comprise part of the natural particulate component of airborne
30 material inhaled and ingested in both rural and coastal settings (Verrault et al., 2008; Whon et al.,
31 2012).
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35 A considerable portion of the dissolved organic carbon (DOC) content of seawater is composed of
36 viral material (Griffen et al., 2003; Steward et al., 2013; Wilhelm & Suttle, 1999; Williamson et al.,
37 2008). Much of this viral content is phage material that infects marine phytoplankton but will also
38 include pathogens from sewage and farmland runoff and marine snow (Shapiro et al., 2014).
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42 Replication of mammalian DNA viruses requires that they gain control of key cellular signalling
43 pathways that affect broad aspects of cellular macromolecular synthesis, metabolism, growth and
44 survival (Krajcsi & Wold, 1998). The PI3K–Akt–mTOR pathway is one such pathway; and DNA
45 viruses have evolved various mechanisms to activate this pathway in order to obtain the benefits of
46 Akt activation, including the maintenance of translation through the activation of mTOR (Buchkovich
47 et al., 2008; Krajcsi & Wold, 1998). However, viruses must overcome the inhibition of this pathway
48 that results from the activation of cellular stress responses during viral infection, although multiple
49 mechanisms have evolved to circumvent inhibitory stress signalling.
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57 **5. SUMMARY & CONCLUSIONS**

1 Many airborne bioactive biogenic chemicals produced by plants, algae, fungi and bacteria are
2 inhaled/ingested by the human populations of rural and coastal areas (Table 1). The concentrations of
3 these chemicals will be low; however, fairly continuous exposure to a diversity of bioactive chemicals
4 may be responsible for inhibition of the mTORC1 component of the PI3K/Akt/mTOR cell signalling
5 pathway. Such a reduction in the activity of the mTOR pathway will probably confer pleiotropic health
6 benefits (Fig. 3; Laplante & Sabatini, 2012).
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10 Ensuing benefits will include a reduction in inflammatory processes that can contribute to
11 cardiovascular disease, neurodegenerative diseases, depression and age-related cancers (Fig. 3).
12 Additional benefits may involve activation of the so-called sirtuin longevity genes (Salminen &
13 Kaarniranta, 2009a). If empirical measurements of the mTOR pathway and other related signalling
14 processes support the hypothesis developed in this paper, then it may be possible to mimic some of
15 the health benefits of living close to the natural environment.
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20 Cytoprotective autophagy is likely to be a key player in any health benefits resulting from interactions
21 with phytochemicals and other products that trigger the signalling pathways for this process. Currently
22 there are a number of drugs in everyday use, such as aspirin (a polyphenol), metformin, and Torisel
23 that are inhibitors of mTOR and inducers of autophagy (Fig. 1; Ferrari et al., 2011; Zhang et al., 2011;
24 Zhou et al., 2010). These compounds are termed rapalogues because they mimic the mTOR inhibitor
25 rapamycin; and considerable interest in mTOR inhibitors is being exhibited by the pharmaceutical
26 industry in the quest for caloric-restriction (CR) mimetic drugs (Davinelli et al., 2012; de Magalhães et
27 al., 2011).
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33 It is highly probable that modulation of cell signalling (if confirmed) of the type described above is only
34 one of a number of potentially interactive factors involved in the observed health benefits, including
35 psychological effects, exercise, more effective immunoregulation, vitamin D and exposure to sunlight,
36 as well as dietary uptake of bioactive phytochemicals (Cox et al., 2014; Del Rio et al., 2013; Depledge
37 et al., 2013; Lisse & Hewison, 2011; Maas et al., 2006; Pandey & Rizvi, 2009; Pearce & Cheetham,
38 2010; Rook, 2013; Seedorf et al., 2014; Smillie et al., 2011; Wheeler et al., 2012; White et al., 2010,
39 2013; Wu & Sun, 2011). Figure 3 shows a comparison of the potential explanatory capacity of each of
40 the three hypotheses in the context of observable health benefits from exposure to green-blue space.
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46 There is evidence that many dietary biogenic compounds, particularly polyphenols, exert their
47 biological effects through synergistic interactions (Kennedy & Wightman, 2011). Other cell signalling
48 components, not discussed in this paper, are targeted as well by dietary polyphenols, including
49 MAPK/ERK (related to cancer), COX-2, AMPK, etc. so these will also need to be considered in the
50 context of airborne phytochemicals (Del Rio et al, 2013; Khan et al., 2006; Rahman et al., 2006;
51 Ramos, 2008).
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56 Finally, does living in the modern built environment constitute a significant change of airborne milieu
57 for humans; and should the natural environment be considered “**the norm**”, as this is what hominids
58 and hominins, and specifically humans, have been exposed to for most of their evolution?
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Consequently, is the increase in wellbeing observed in the natural environment an improvement or should it be considered as the baseline state? In the urban environment there will be a deprivation of airborne exposure to a considerable diversity of biogenics mostly targeting the PI3K/Akt/mTOR cell signalling pathway; and often an increase in exposure to man-made contaminant xenobiotics. A crucial question for future research is whether the concentration of bioactive chemicals in natural aerosols is sufficient to interact effectively with cell signalling, in the manner hypothesised in this paper. Certainly airborne phytochemical allergens can interact with cell signalling systems to elicit a hypersensitive reaction from the immune system (Laiidi et al., 2003; Postolache et al., 2007). Consequently, future characterisation of the cell signalling related bioactivity of phytochemicals and other biogenic compounds in natural aerosols will be critical in determining the validity of this “biogenics” hypothesis, as has already the case with airborne marine algal toxins (Cheng et al., 2005a, b, 2007).

6. PROSPECTUS

Based on the discussion in this paper, it is proposed that future epidemiological investigations on the health benefits of natural environments should target the activities of the various kinases in the PI3K/AKT/mTORC1 systems and biomarkers of autophagy for selected urban, rural and coastal populations in order to test this “biogenics” hypothesis. This type of data probably already exists in some epidemiological databases (Harries et al., 2012), but has not yet been tested in the context of the question posed in this paper.

Experimental and observational testing of the “biogenics” hypothesis will be required to complement any supporting epidemiological data that may emerge. A suggested way forward is as follows:

- detailed seasonal sampling and analysis to characterise airborne biogenic compounds is needed both from urban and rural/coastal environments at various latitudes
- determination of bioactivity of the airborne biogenics identified will need to be confirmed in laboratory animal tests involving exposure to phytochemical aerosols
- testing for endpoints associated with the PI3K/Akt/mTOR systems and PTEN, as well as biomarkers for autophagy (e.g, Atg proteins – Lamb et al., 2013), apoptosis, inflammation, oxidatively damaged proteins (e.g., protein carbonyls and aggregates, ceroid lipofuscin), and higher level health indicators
- transcriptomic, proteomic and epigenomic studies in experimental animals in order to develop a framework of mechanistic understanding of molecular and cellular action of biogenic chemicals

- pre-clinical tests conducted in human volunteers with endpoints selected on the basis of the results from animal exposures.

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4 Finally, if this hypothesis is supported by the data, then public health strategists and urban planners
5 will need to take it into consideration for the improvement of the health and wellbeing of urban
6 dwellers. Essentially, is it possible to effectively “bottle” the benefits of natural green-blue space?
7 Perhaps this could be facilitated by adding natural phytochemicals to aerosols in the home, and in
8 large public spaces such as shopping malls, theatres and cinemas. Also, the role of exercise (an
9 inhibitor of mTORC1 by increasing the activity of AMPK – see Fig. 1) needs to be considered as an
10 interacting factor, as this will increase respiration and, hence, inhaled and ingested airborne biogenics
11 (Dreyer et al., 2006). Currently, there is very extensive consideration of the health-related properties
12 of bioactive phytochemicals in the diet; and supplementing these in foodstuffs may provide an
13 alternative route to attain the health benefits discussed above (Del Rio et al., 2013; Kennedy &
14 Wightman, 2011; Khan et al., 2006; Kim et al., 2013; Rahman et al., 2006; Ramos, 2008).
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15 **Figure Captions**

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20 **Fig. 1.** Simplified diagram of the multiple cell signalling pathways involving mTOR (see Laplante &
21 Sabatini, 2009, 2012, for a more extensive chart of mTOR related cell signalling). Overactivity
22 of mTORC1 is believed to trigger inflammatory processes which can result in pathological injury
23 and processes leading to many cancers and degenerative diseases. PI3K -phosphatidylinositol-
24 3 kinase; PIP₃ - phosphatidylinositol 3,4,5 trisphosphate; Akt - serine/threonine kinase Akt or
25 protein kinase B (PKB); mTORC1 - mammalian target of rapamycin complex 1; NF-κB - nuclear
26 factor kappa-light-chain-enhancer of activated B cells; PTEN - phosphatase and tensin
27 homolog; AMPK - 5' adenosine monophosphate-activated protein kinase p27 - cyclin-
28 dependent kinase inhibitor; ROS – reactive oxygen species. Activation ↑; inhibition ⊥.
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37 **Fig. 2.** Summary diagram of the multiple cellular protective functions of autophagy in normal and
38 diseased cells. Modified from Eskilenin & Saftig (2009).
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44 **Fig. 3.** Summary diagram of the psychological, immunoregulation and biogenics explanations for the
45 health benefits accrued from exposure to rural and coastal environments (Green-Blue Space;
46 adapted in part from Rook (2013). * **Treg** - the regulatory T cells (Treg), formerly known as
47 suppressor T cells, are a subpopula on of T cells which modulate the immune system,
48 maintain tolerance to self-an gens, and abrogate autoimmune disease.
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Table 1. Summary of various types, sources and targets/effects of potential airborne biogenic chemicals that could influence human health if ingested (see references below).

<i>Biogenic product</i>	<i>Origin</i>	<i>Potential biological target or effect</i>
Bacterial toxins	Soil particles, seawater aerosols	Inhibition of specific cell signalling systems (PI3K, mTORC1)
Cyanobacterial toxins	Seawater aerosols, soil particles	Inhibition of specific cell signalling systems (PI3K, mTORC1)
Antibiotics	Soil particles	Inhibition of specific cell signalling systems (PI3K, mTORC1)
Polyphenolics (flavonoids, anthocyanins, procyanidins, proanthocyanidins, catechins, tannins, humics, etc.)	Soil particles, higher plant abrasion particles, pollen grains, fern spores, fungal spores, macroalgal fragments (brown, green & red)	Inhibition of specific cell signalling systems (PI3K, Akt, mTORC1), PTEN, MAPK/ERK (related to cancer), COX-2, AMPK autophagy, apoptosis, anti-cancer properties, cardiovascular protection, enhanced brain function
Mycotoxins	Fungal spores, soil particles, hay-derived particles	Inhibition of specific cell signalling systems (PI3K, mTORC1)
Pyrrolizidine alkaloids	Higher plant abrasion particles, pollen grains	Carcinogenic, tumorigenic & anti-cancer properties
Terpenoids (monoterpenes, diterpenes, triterpenes)	Higher plants (volatiles)	Apoptosis, autophagy, others
Viral particles or protein fragments	Marine viruses in airborne aerosols	Immune system, inhibition or activation of PI3K, mTORC1, mTORC2

Table 1 References: - Abrahams, 2002; Al-awar et al., 2004; Arafa et al., 2011; Ballou & Lin, 2008; Banerjee et al., 2014; Beevers et al., 2013; Bennick, 2002; Bharate et al., 2012, 2013; Bode & Dong, 2013; Boopathy & Kathiresan, 2010; Buchkovich et al., 2008; Campos et al., 2008; Chai et al., 2012; Chen et al., 2014; Cheng et al., 2005a, b, 2007; Christensen et al., 1999; Cock, 2013; de las Heras & Hortelano, 2009; Del Rio et al., 2013; de Oliveira et al., 2013; Delmas et al., 2011; Després et al., 2012; Duke, 2011; Farmer & Ryan, 1990; Farrand et al., 2014; Ferrari et al., 2011; Fischer & Dott, 2003; Fleming et al., 2005; Fleming et al., 2007, 2014; Frohlich-Nowoisky et al., 2009; Gantar et al., 2012; Ghoshal & Saoji, 2013; Goufo & Trindade, 2014; Hooper et al., 2010; Huang et al., 2013; Hurd, 2013; Ibañez et al., 2012; Inglés et al., 2014; Jeong et al., 2013; Johnson et al., 2009; Kaur et al., 2013; Kelsey et al., 1978; Kennedy & Wightman, 2011; Kong et al., 2011; Korsnes, 2012; Kourtchev et al., 2013; Krajcsi & Wold, 1998; Kuitert & Denneman, 1987; Kusuhara et al., 2012; Lamming et al., 2013; Lee et al., 2012; Lee et al., 2010; Malloy & Marr, 1997; Matricardi et al., 2000; Matsunaga et al., 2011; Mitchell & Popham, 2008; Møller et al., 2004; Moore et al., 2013, 2014; Munday, 2013; Murakami, 2013; Nagle & Zhou, 2009; Nam, 2006; Okuda et al., 2005; Ozkan et al 2015; Pandey & Rizvi, 2009; Park et al., 2010b; Postolache et al., 2007; Rogge et al., 1993c; Rook, 2014; Russo et al., 2014; Salminen et al., 2008; Sarojini et al., 2012; Shelton et al., 2002; Son et al., 2013; Stegelmeier et al., 1999; Sundin & Hentosh, 2012; Syed et al., 2013; Tan et al., 2014; Thoppil & Bishayee, 2011; Tsunetsugu et al., 2010; Van Aller et al., 2011; Wang, 2008; Wang et al., 2014; Williams, 1963; Womiloju et al., 2003; Xie et al., 2013; Zhang et al., 2012; Zhou et al., 2010.

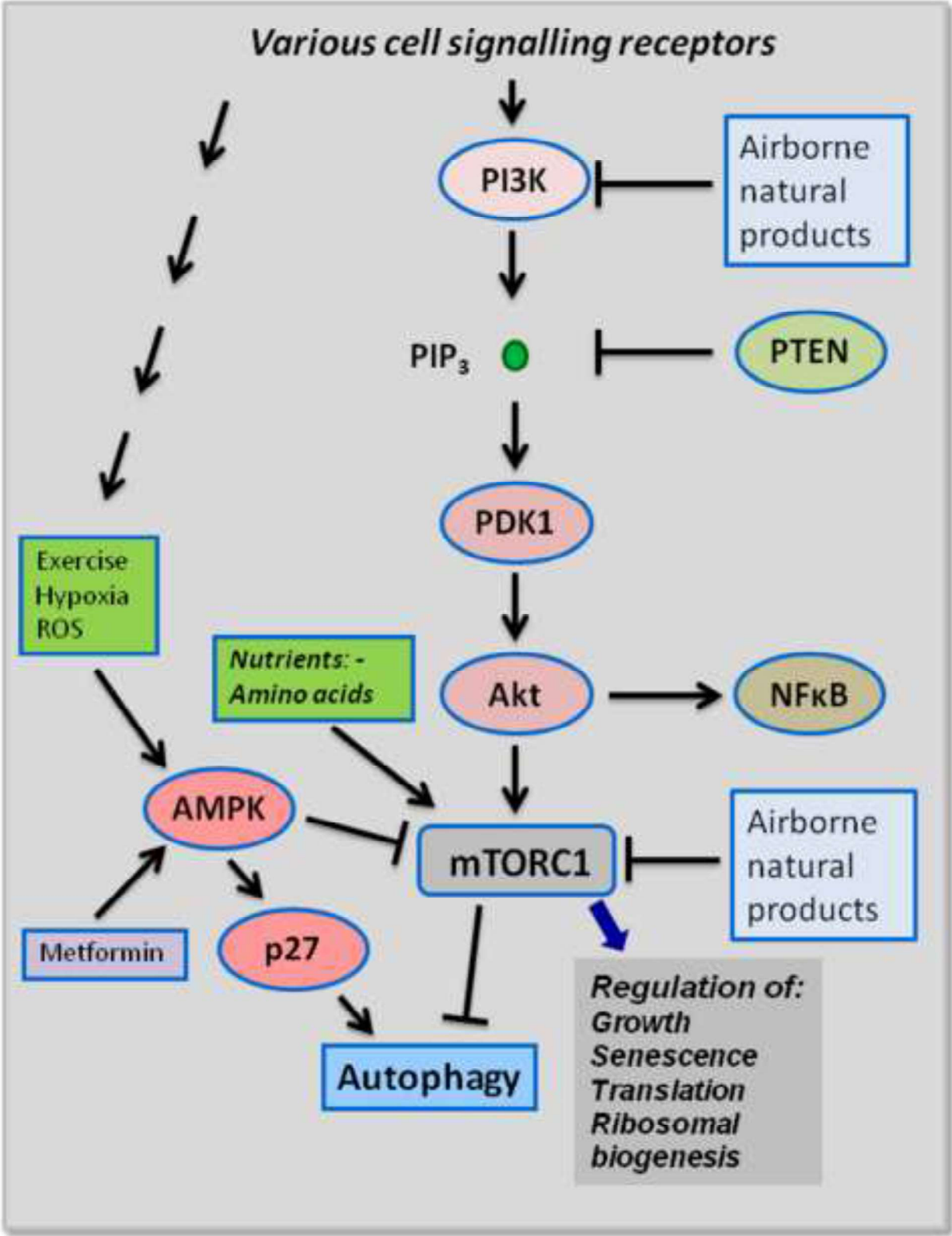


Figure 1

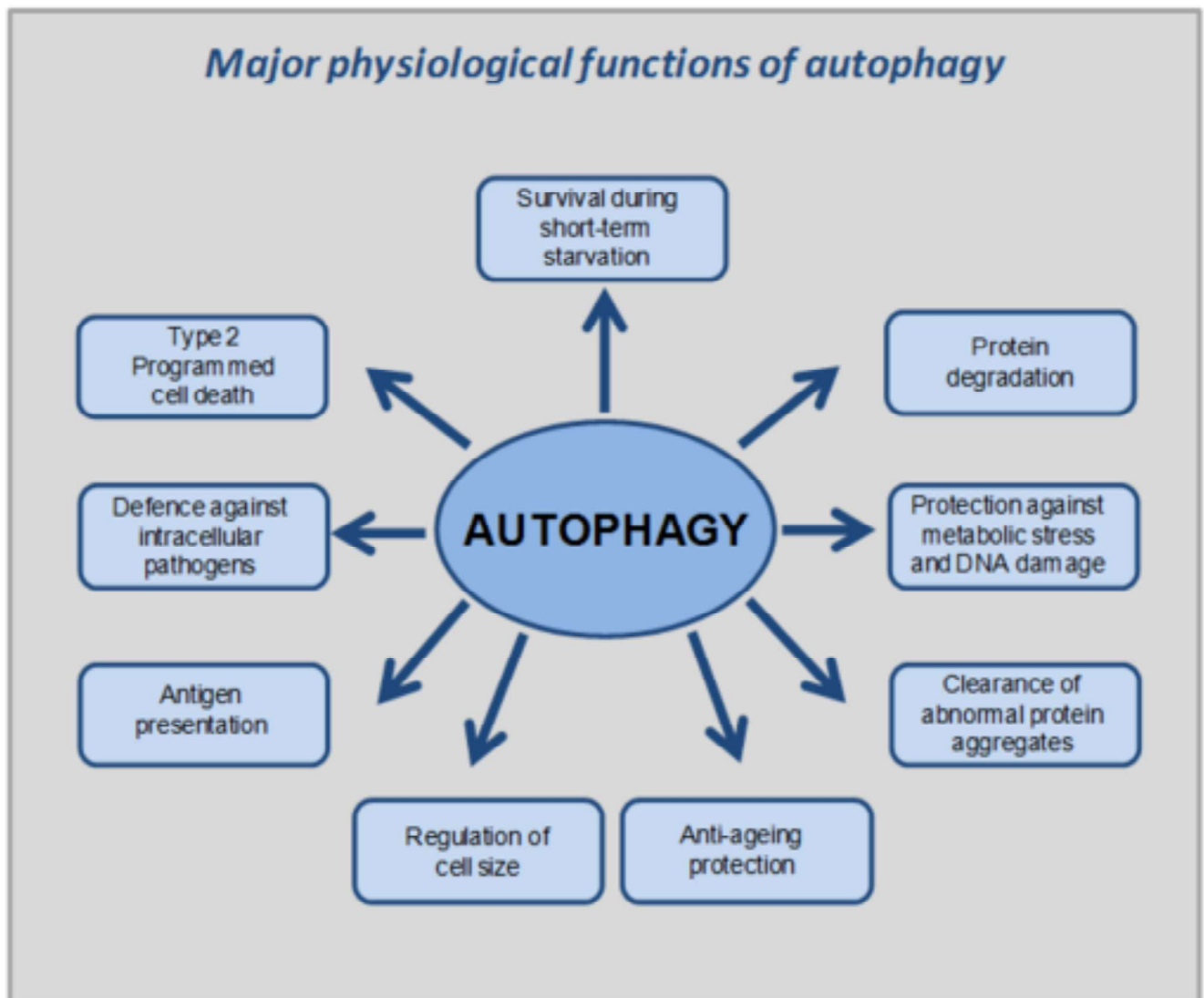


Figure 2

GREEN-BLUE SPACE effect	Psychological Hypothesis	Immunoregulation Hypothesis	Biogenics Hypothesis
Walking and recreation in green-blue space	Evolutionarily determined psychological need (habitat selection?)	Evolutionarily determined need for diverse microbial input to immune system	Evolutionarily determined need for diverse exposure to biogenics
Social interactions	Build social capital	Exchange of microbiota	Exchange of microbiota-associated biogenics
Sport & exercise	"Hunter-gatherer" activity; health benefit; weight loss	Exchange of microbiota; more Treg ⁺ ; immunoregulation.	Exchange of microbiota-associated biogenics; increased inhalation/ingestion of biogenics; hypoxia and ROS induced mTOR-inhibition mediated autophagy
Sunlight	Combat Seasonal Affective Disorder (SAD)	Vitamin D and nitric oxide (NO) improve immunoregulation	Enhanced vitamin D; vitamin D receptor (VDR) induced autophagy
CLINICAL OUTCOME			
Fewer deaths, less cardiovascular disease, less neurodegeneration, less cancers?, increased longevity?	Relaxation and exercise?	Low CRP; low inflammation	Inhibition of PI3K/Akt/mTOR; activation of PTEN; reduced ROS; enhanced cellular housekeeping (autophagy); improved innate immunity; Treg ⁺ immunoregulation; low inflammation; enhanced brain function; anti-cancer; anti-ageing effects; more stress resilience
Less depression	Relaxation; restoration; social capital?	Lower cytokine response to stress; more stress resilience	Inhibition of PI3K/Akt/mTOR; low inflammation; more stress resilience

Figure 3

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