

Review

Gene–Environment Interactions and Stochastic Variations in the Gero-Exposome

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Abstract

The limited heritability of human life spans suggests an important role for gene–environment ($G \times E$) interactions across the life span (T), from gametes to geronts. Multilevel $G \times E \times T$ interactions of aging phenotypes are conceptualized in the *Gero-Exposome* as Exogenous and Endogenous domains. Stochastic variations in the Endogenous domain contribute to the diversity of aging phenotypes, shown for the diversity of inbred *Caenorhabditis elegans* life spans in the same culture environment, and for variegated gene expression of somatic cells in nematodes and mammals. These phenotypic complexities can be analyzed as 3-way interactions of gene, environment, and stochastic variations, the *Tripartite Phenotype of Aging*. Single-cell analyses provide tools to explore this broadening frontier of biogerontology.

Keywords: *APOE*, Exposome, Gerogens, Tripartite Phenotype

Background

The low heritability of life spans has long perplexed biogerontologists. For human twins and the inbred worm, the heritability of life spans is less than 35%, and may be below 10% (1–6). Despite their 1000-fold differences, the variance of human and *Caenorhabditis elegans* life spans is similar when scaled to life span as the coefficient of variation (COV) (3). We propose that the limited heritability of aging patterns and longevity in humans is an outcome of gene–environment ($G \times E$) interactions for individual longevity haplotypes, together with stochastic (chance) somatic variations. For inbred nematodes in the same environment, the individual differences represent multilevel stochastic variations (2,7,8). For humans, the 20-year gap of longevity across socioeconomic status (9) involves modifiable environmental factors of diet, physical activity, and inhaled toxins from air pollution (AirPoll) and cigarette smoke (CigS). While many longevity genes are known, their $G \times E$ over time (T) has received less attention and the contribution of stochastic variations is undefined. Y chromosome genes also have undefined $G \times E \times T$ interactions on longevity.

The Gero-Exposome

$G \times E \times T$ is considered during the human life course in the framework of the *Gero-Exposome* (Figure 1). The exposome concept was developed by Wild in 2005 and 2012 for cancer epidemiology (10,11) and has been widely applied (12,13). The limitations of the “one-by-one” analysis of carcinogens demanded a more comprehensive analysis of environmental and lifestyle factors. Wild identified 3 domains in the exposome: the *Exogenous Macrolevel Exposome* (rural vs urban; social stratification; ambient toxins from CigS and AirPoll); the *Exogenous Individual Exposome* (diet, infections); and the *Endogenous Exposome* (biomes of gut and airways, fat depots, tissue injuries) (10,12). We applied Wild’s concept to Alzheimer’s disease (AD) in the “AD-Exposome” (12) to analyze multiple levels of pathogenesis for $G \times E \times T$ (12), and in the Paleo-Exposome for $G \times E$ in the evolution of human longevity (13). We suggest explicit consideration of stochastic components that were often understood as implicit within E in the traditional binary formulation of $G \times E$. The Endogenous Exposome should also include cell-to-cell variations of gene

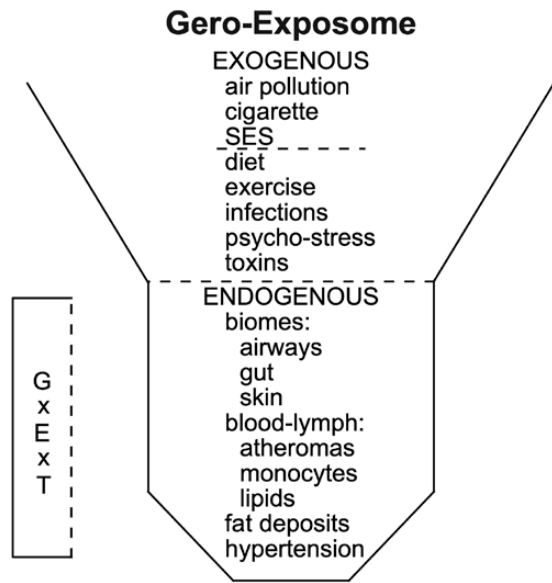


Figure 1. The Gero-Exposome with exogenous and endogenous components. $G \times E \times T$ = interactions of gene by environment over age and time, from the prefertilization oocyte into later ages; SES = socioeconomic status. Finch and Kulminski (12) gives further details of the Exogenous and Endogenous Exposomes.

expression described as “variegated gene expression” (14). This innovative study identified human genes that controlled the variability of expression, measured as COV, for *SIRT1*, a longevity-related gene. Future studies of variegated gene expression should consider expression of *APOE* and its neighboring genes, whose haplotypes influence heart disease, obesity, hypertension, AD, and longevity (15). Age-related increase of somatic cell mutations and epigenomic modifications of DNA and histones will add noise to $G \times E \times T$.

Fat depots are important to the Endogenous Gero-Exposome because of their contribution to systemic inflammation: IL-6, TNF α , and C-reactive protein are higher in venous blood from fat depots than in arterial blood (16–18). Inflammatory secretions emanate from the macrophages surrounding adipocytes that increase with obesity (19). Fat depots also secrete C-reactive protein (CRP), assessed in obese patients before and after bariatric surgery (20). The antibacterial CRP is also made by the liver during acute-phase inflammatory responses. *APOE* alleles influence obesity and neurodegeneration in mouse models, discussed below. Both exogenous and endogenous stressors can induce inflammatory damage with $G \times E$ interactions, as shown for the influence of *APOE* allele on vascular and neurodegenerative diseases (15,21). Obesity increases the risk of AD (22) and degeneration of brain myelin (white matter) (23), and is augmented by *APOE4*. Transgenic mice fed fat show $G \times E$ for the human *APOE4* with accelerated brain amyloid deposits (24,25). The gut biome also varies by *APOE* allele (26).

Environmental toxicants that influence adult health were identified in the HELIX project (Human Early Life-Exposome). Childhood obesity was increased by maternal CigS (27), while children’s telomeres were shortened in white blood cells by both elevated urban AirPoll (28) and secondhand CigS (29). AirPoll and CigS promote obesity and elevated blood glucose and lipids (*endogenous individual domain*) that are risk factors for atherosclerosis, various

cancers, hypertension, and AD and are preventable causes of premature aging (30).

Ambient Toxins of the Exogenous Macro Exposome: AirPoll and CigS

Inhaled toxins from AirPoll and CigS are associated with excess mortality and shortened longevity. In 2019, AirPoll and CigS were attributed to 16 million excess deaths worldwide, which is 2-fold more than the 8 million deaths attributed to, infections and road injuries, the next ranked causes of death (30). Mortality from AirPoll and CigS is likely to have increased in 2020 because coronavirus disease 2019 (COVID-19) mortality is increased by CigS (31) and elevated AirPoll (32).

For AD, CigS accounts for 11% U.S. cases, and 14% worldwide (population attributable risk) (33). Cognitively normal smokers older than 60 years incur accelerated brain aging from CigS, with greater accumulation of brain amyloid (34) and earlier atrophy of cerebral cortex (35). Secondhand smoke also increased risk of dementia and accelerated cognitive decline in large population studies from the United States (36) and China (37,38). AirPoll accelerates brain atrophy and cognitive decline (39,40), and increases the risk of AD (39,41,42).

AirPoll and CigS may be considered as *gerogens* as they promote pathogenesis of the major morbidities of aging: atherosclerosis, cancer, and dementia (43). For heart disease, lung cancer, and cognitive decline, AirPoll and CigS synergize with super-additivity (44–46). Women have greater neurological vulnerability to AirPoll by 3% higher risk than men of AD and Parkinson disease, shown for 63 million U.S. Medicare older people in the largest population-based study to date (42).

AirPoll Neurotoxicity of $G \times E$ in Mouse Models

Several mouse models of AirPoll show $G \times E$ for *APOE* alleles and sex. For Rodent exposures to AirPoll, our lab has used a nanoscale subfraction of particular matter (nPM) collected from a Los Angeles freeway designated here as AirPoll-nPM; other labs use direct traffic exposure, or AirPoll components such as ozone (O_3) or diesel exhaust particles (47). Mice transgenic for human familial AD-dominant mutations respond to chronic AirPoll-nPM with increased soluble A β 42 peptide and increased plaque load (Figure 2A) (39,48). Subcellular mechanisms include increased pro-amyloidogenic processing of the amyloid precursor protein (APP) in lipid rafts (Figure 2B).

Older women who carry *APOE4* are at higher risk of AirPoll-associated dementia (39). We find corresponding sex differences for *APOE* alleles in mouse brain transcriptome responses to AirPoll-nPM (49). Only female *APOE3*-TR mice responded to AirPoll-nPM in genes for production of the amyloid A β peptide (*APP*, *Bace11*, *Psen1*) and for A β phagocytosis (*Vav2*, *Vav3*) (Figure 2B). This suggests that *APOE3* carriers efficiently clear amyloid oligomers, which may counteract AirPoll, consistent with impaired A β clearance in *APOE4* carriers. Male *APOE*-TR did not respond to AirPoll-nPM in amyloid metabolic gene pathways. The female excess risk for AD decline may be due to sex differences in brain genomic response to AirPoll, with 2-fold more gene responses and different pathways in young female mice than in male mice (49). Similarly, ozone exposure caused memory decline in young male *APOE3*-TR mice, but not in *APOE4* mice (50). The higher baseline levels of enzymes for

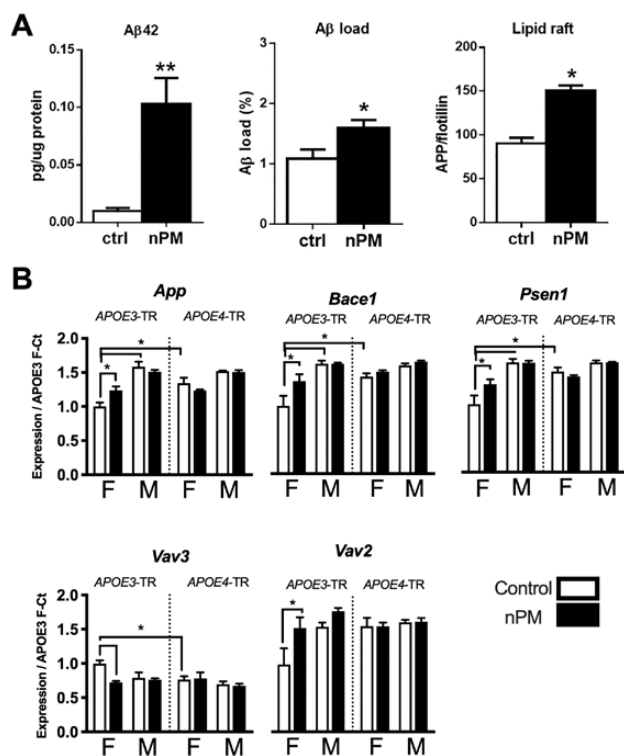


Figure 2. AirPoll-nPM induces amyloidogenic responses in mouse cerebral cortex after exposure for 8–10 wk of high traffic levels. (A) Amyloidogenic responses of J20 male mice carrying APP^{sw} (familial AD gene) showing increase of soluble Aβ₄₂ and Aβ plaque load (39), and increased lipid raft levels of amyloid precursor protein (APP) (39). **p* < .05, ***p* < 0.01 (B) Amyloid metabolic gene response of *APOE*-TR mice carrying human *APOE3* and *APOE4* alleles by targeted replacement (no familial AD genes) (49). * *p* < .05 in ANOVA test after FDR multiple test correction. AirPoll = air pollution; nPM = nanoscale subfraction of particular matter.

oxidative stress response in *E4* males suggest a ceiling effect for their lack of response to ozone. These findings suggest epidemiological studies.

Two transcription factors, NRF2 and NFκB, showed the same pattern for *APOE4*-TR of baseline differences and lack of responsiveness to AirPoll. More than 80 genes downstream of NRF2 responded to AirPoll in mouse cerebral cortex. AirPoll-nPM induced nuclear translocation of NRF2 in liver and lung, as well as brain (51), suggesting bodywide systemic responses. While aging also increased NRF2 expression (51), middle-aged mice had minimal NRF2 response to AirPoll (52). This apparent ceiling in AirPoll response effect extends to neurite atrophy in hippocampal CA1 neurons (52,53). The selective neurotoxicity of CA1 neurites to AirPoll-nPM parallels the selective CA1 neurodegeneration during AD.

We anticipate complex interactions of sex and aging for *APOE* alleles and other AD risk genes with AirPoll that may differ by age. A causal chain of responses to AirPoll across the human life course may include the following: (i) high baseline oxidative stress in aging or *APOE4* individuals; (ii) AirPoll-nPM excessive induction of NRF2 antioxidant responses that increase the nuclear NRF2 baseline; (iii) increase of NFκB baseline; and (iv) increasing neurological damage, with diminished response to exogenous and endogenous stressors. This pattern occurred in multiple organs of middle-aged mice chronically exposed to nPM (51). The developmental impact of AirPoll and CigS is discussed below.

Cigarette Smoke

G × E interactions with CigS neurotoxicity are shown in 2 studies. Cognitively normal *APOE4* smoker aged 56–94 had greater brain amyloid and deficits in glucose utilization than E3 smokers; deficits in memory and auditory-verbal learning also differed by *APOE* (Alzheimer Disease Neuroimaging Initiative) (34). Middle-aged twins also showed G × E for CigS in cerebral cortex area (Veterans Twin Study of Aging) (54). Smoking history has been neglected by most genetic studies of dementia, and of other genes that influence longevity.

Rodents exposed to CigS confirm human findings. Mice transgenic for familial AD genes and exposed to chronic CigS accumulated 50% more brain amyloid and phosphorylated tau (55). Similarly, wild-type rats responded to CigS with increased AD biomarkers of sAPPa and phospho-tau (56). Reactive glia were increased in both models, as observed for AirPoll-nPM.

Sex is a neglected factor in human and rodent studies of CigS. In collaboration with demographer Eileen Crimmins, we showed that female heavy smokers had a higher risk of earlier age of death and stroke than males of the Health and Retirement Study (57). *APOE* alleles were not available.

AirPoll and CigS independently shorten the life span with dose dependence and promote many of the same aging processes. We asked if these gerogens might share some of the same gene targets by comparing gene SNPs of long-lived smokers with genes activated in mouse brain responses to AirPoll. In 2016, Levine and Crimmins (58) identified 215 SNPs in long-lived smokers of the Health and Retirement Study, a U.S.-wide longitudinal study of health and aging. The groups compared were smokers who survived to age 80 versus smokers up to age 70, with Caucasian predominance. The long-lived smokers had mortality rates similar to same-age “never smokers.” We find considerable overlap of genes identified by SNPs in smoking-survivors with AirPoll-nPM-responding genes in mouse brain (Figure 3). Initial analysis showed that most (63%, 136/215) of the genes with SNPs in cigarette-survivor also respond to AirPoll-nPM in mouse (49). Functional analysis of genes associated with these 215 SNPs shows enrichment for shared pathways associated with immune response, oxidative stress, and development. SNPs are located near or within known human longevity genes (FOXO3, HLADR1). Twenty shared genes have association with AD (eg, GAD2, GRIN2A, and GRIN2B). The 2016 gene database of the Health Retirement Survey did not include *APOE* alleles. Many other G × E interactions of airborne toxins with *APOE* alleles and sex may shape the healthspan and life span.

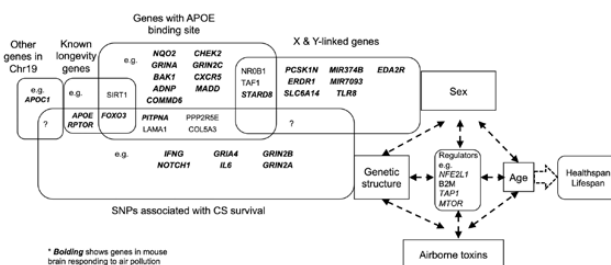


Figure 3. Schema for interactions of genetic background, sex, airborne toxins, and age on individual health span and longevity. Bolding identifies genes that responded to AirPoll in the mouse brain (49,53,60) that are shared with older surviving smokers (58). AirPoll transcriptome- and CigS-associated SNPs show extensive overlap, suggesting shared mechanisms. AirPoll = air pollution; CigS = cigarette smoke.

The *APOE* gene does not act alone as an AD risk factor on chromosome 19.3. Kulminski et al. has identified AD risk-haplotypes in more than 5 neighboring genes (59). The *APOE* gene clusters of mouse and human share many genes, but with inverted synteny (60). While its genetic variants have received the most attention, little is known of how the *APOE* cluster genes respond to environmental factors. Initial studies of mouse brain and archived data show that *APOE* cluster genes are highly responsive to components of AirPoll (60). Mouse cerebral cortex responded to AirPoll-nPM with increased *ApoE* mRNA levels together with various combinations of *Tomm40*, *Apoc1*, and other gene neighbors (Figure 4A). Human brain cDNA libraries also showed co-expression of *APOE* cluster genes, differing by sex (Figure 4B) and age with brain region specificity (Figure 4C). DNA methylation in the *APOE* cluster shows a complex epigenetic architecture that differs for AD and the cognitively normal participants (61).

The diverse *APOE* cluster responses to AirPoll components were explored with archived data from humans and rodents (60). Mouse lung responded differently from brain with other *ApoE* cluster subsets to coal tar and another AirPoll sample different from that used in our studies. Coal tar increased mRNAs of *Apoc1*, *ApoE*, and *Nectin2*, while AirPoll induced *Apoc1*, but not *Tomm40*. Antioxidant and inflammatory responses of other chromosomal genes include the expressions of *Nqo1* and *Il1b*, which also responded to AirPoll-PM in Nrf2-regulated phase II gene expression in lung and brain (51). These findings give insights for the heterogeneity of AD risk from *APOE4*. Divergent patterns of co-expression of *APOE* cluster genes to the above AirPoll may arise from variations in local AirPoll chemistry for oxidative activity, despite the same density of AirPoll particles (62,63).

Developmental Impact of AirPoll and CigS

The Gero-Exposome (Figure 1) includes developmental exposures in the Exogenous domain. The analysis is necessarily multigenerational because human primary oocytes are fully formed before birth; thus,

our prenatal oocyte was exposed to our grandmaternal environment (64). Multigenerational toxic influences are documented for CigS and lead (Pb) gestational exposure in rodent models (43,65). Robust effects in the first generation include elevated brain cytokines, neuronal deficits, and impaired glucose metabolism, together with increased depressive behaviors shown by us (66) and others (67,68). The male bias of many rodent gestational exposures parallels the male bias of autism, which is increased by early exposure to AirPoll (69). These sex differences anticipate other $G \times E \times T$ interactions for the impact of childhood obesity on later-life cardiovascular and neurodegenerative diseases. *APOE* alleles have not been studied for the impact of CigS or AirPoll on pre- or postnatal development. Several examples illustrate the developmental harm of CigS and AirPoll. Fetal growth is consistently impaired by maternal smoking. Third-trimester exposure to maternal smoking shortened femur length and skull width (biparietal diameter; meta-analysis of 10 000 pregnancies in 16 studies) (70). In turn, maternal smoking is associated with higher adult body mass index (71), a risk factor in many age-related pathologies. There is a likely convergence of CigS and AirPoll in fetal growth retardation (72).

Epigenetic effects of maternal smoking include postnatal DNA methylation, robustly shown for *GFII1*, a transcriptional repressor which was hypomethylated at 8 CpG sites in adult children of maternal smokers (meta-analysis of 18 212 individuals from 17 populations) (73). Several hypomethylated *GFII1*-CpGs are associated with low birth weight, and adult adiposity and hypertension, which are AD risk factors. Whole-genome methylomes (bisulfite cleavage) show additional DNA methylation responses to maternal smoking in enhancers and other gene regulatory domains (74,75). Similarly, the gene promoter of *SLC7A8*, an amino acid transporter, had parallel changes of DNA-CpG sites in cord blood and adults of the Maternal and Child Health Study (75). Placental DNA methylation of *CYP1A1* (detoxification gene) may also respond to maternal smoking (76,77).

The risk of childhood obesity is increased by maternal smoking. A meta-analysis of 236 687 children worldwide showed robust associations of maternal smoking during pregnancy with overweight (odds ratio [OR] 1.37) and obesity (OR 1.55) (78). Moreover, the combination of secondhand CigS and AirPoll promotes childhood obesity (44). In turn, childhood obesity increases risk for adult dyslipidemias that promote cardiovascular disease (79). As noted above, fat depots secrete inflammatory proteins, worsened by obesity. *APOE* alleles were not included in these studies.

Resolving the complex $G \times E$ relationships of AirPoll would be facilitated with a high-throughput, short-duration screening model. We developed the nematode *C. elegans* as a new model for developmental influences of AirPoll (80). Concentrations of AirPoll-nPM in culture media were identified that did not alter survival curves. Initial studies showed responses of *C. elegans* to AirPoll-nPM in the culture media that corresponded to findings in rodents. For example, rapid responses to 1 hour of nPM exposure induced genes for oxidative stress responses (eg, *gst-4*), inflammation (eg, *tol-1*), and of the human AD pathway (eg, *apl-1/APP* homolog, and *sel-12/PSEN1* homolog) (80). These rapid responses paralleled the rapid increase of A β 42 in mouse brain from 3-hour exposure to nickel nanoparticles in FVBM mice (47,81). RNAi knockdown of the NRF2 homolog *skn-1* eliminated the long-term developmental and life-span hormetic effects of early-life acute exposure to AirPoll-nPM (80). One-hour exposure of young adult worms to 50 μ g/mL AirPoll-nPM in L1 and day 1 adulthood increased life span by 1.1 days, which was blocked by *skn-1* RNAi (Figure 5A). Developmental exposure at L1

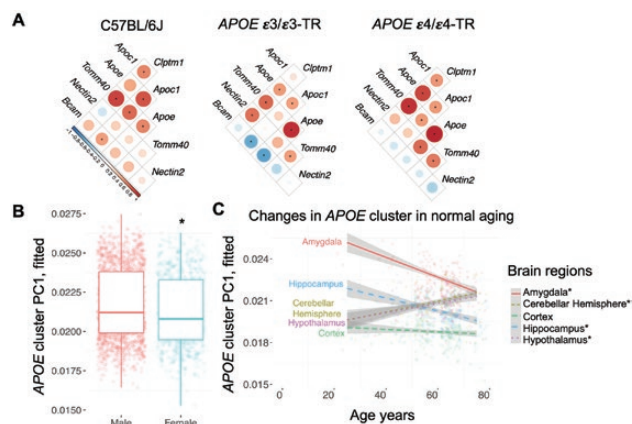


Figure 4. *APOE* gene cluster expression in mouse and human brain. (A) Heat maps showing transcriptional response of the mouse *ApoE* gene cluster to AirPoll-nPM in cerebral cortex, for C57BL/6J (B6) and transgenic for human *APOE* allele, *APOE3-TR* and *APOE4-TR*, both sexes. Principal component analysis of human *APOE* cluster expression for 5 brain regions (321 individuals, GTEx data) shows *APOE* PC1 differed by sex (B) and age (C) with brain region specificity. Figure adapted from Haghani et al. (60). AirPoll = air pollution; CigS = cigarette smoke.

caused smaller-sized adults. Again, the developmental effect of nPM was blocked by *skn-1* knockout (Figure 5B). The pleiotropic effect of SKN-1 activation by AirPoll-nPM is consistent with the metabolic reallocations of *skn-1* gain-of-function mutants that increased longevity at the expense of decreased resistance to pathological bacteria (82). Because oxidative stress from paraquat decreased pathogen resistance, AirPoll may also impair immunity, as indicated by covariance of elevated AirPoll with risk of COVID-19 infections.

These findings merit extension to mouse models of Nrf2 manipulation by drugs and inducible gene knockdown to attenuate AirPoll toxicity. The *hsp-16.2* and *skg* genes are interesting prospects for interactions with AirPoll, and for genes that alter the variability of stem cell number (83). The temperature dependence of life span in *sgk-1(ok538)* (84) would be interesting to study for interactions with AirPoll-nPM. Transgenerational effects of AirPoll may be anticipated from the growing list of environmental toxins and stressors with multigenerational effects that extend 3 or more generations, for example, for maternal exposure of mice to the flame retardant tetrabromobisphenol (85) or Pb (65,86). Mechanisms include altered methylation of DNA in mice (86) and of histones in *C elegans* (87). Other toxicants with experimentally reported transgenerational effects include vinclozolin (88) and other endocrine disruptors. Vinclozolin exposure can also cause “tertiary epimutations” by altering germline DNA methylation and somatic mutations that persist at least 3 generations (88). We anticipate other examples of epimutations from environment toxicants with transgenerational persistence and complex G × E interactions that will threaten future global health.

Stochastic Variation in the Total Phenotype

The unexplained heritability of life spans may also arise from interactions of environmental and stochastic factors with the genome, which we summarize as the Tripartite Phenotype of Aging (Figure 5). Bidirectional arrows indicate their interactions and plasticity of overlap, and extend earlier analyses (2,89,90).

Life span of *C elegans* varies as widely as humans when expressed as COV (3). Despite their isogenic status in the same culture dish, young worms swim at different rates, lay different numbers of eggs, and vary widely in their loss of these functions during aging. The loss of locomotion is attributed to sarcopenia from scattered myocyte cytopathology with loss of myofibrils, while neurons apparently remain intact (7). While these variations remain undefined for sarcopenia, stochastic variations of life spans are better understood for the heat shock gene promoter *hsp-16.2* in benchmark studies by Tom Johnson, Alex Mendenhall,

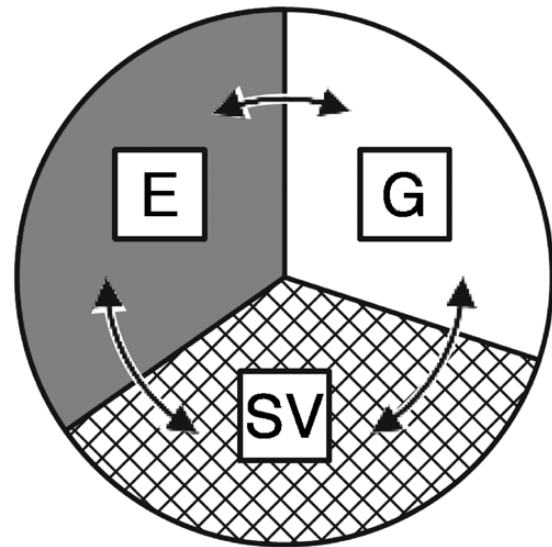


Figure 6. The Tripartite Phenotype: G, heritable genes with variable impacts from the environment (E), in both the Exogenous and Endogenous domains of the Gero-Exposome (Figure 1), and from stochastic variations (SVs) during individual development and stochastic anomalies resulting in postnatal molecular damage, both intracellular and extracellular.

and colleagues (91). The life spans of individual worms scaled with *hsp-16.2* gene expression over a 2-fold range. In contrast, 2 other stress inducible genes (*myo-2* and *mtl-2*) lacked association of expression levels with longevity (92). Locomotor activity paralleled the longevity trends (93), confirming a prior study (7). Genetic manipulations that decreased insulin signaling also decreased life-span COV (94,95).

Subcellular analysis of stochasticity by Mendenhall’s group showed cell-to-cell differences in *hsp-16.2* protein levels of intestine cells of young worms (8). The scale of differences in cell expression for this key chaperone greatly exceeded the intrinsic noise in gene expression, as determined by reporters for each gene. The “variegated gene expression” of mammalian genes in vitro described above was associated with *SIRT1*, a human longevity gene (14). There may be stochastic components in the sex-APOE differences of *Sirt1* expression in brain, which was 50% lower in APOE3 females than for other sex-APOE genotypes (49). A physiology of stochasticity is suggested by the regulation of intestinal cell variations by neurosecretions from thermosensory neurons (94). Further variations may be found in neuronal contacts of *C elegans*. While worms are known for (almost) identical numbers of each cell type, nonetheless, adult individuals vary widely in subcellular location and type of motor neuron synapses, implying variations during development (96,97). Subcellular mechanisms of stochasticity include gene silencing through small RNAi that are transmitted at least 3 generations (98). Stochastic processes have been modeled for individual trajectories of aging (99) and G × E (100) that confirm the large scale of stochastic epigenetic variations during development with later consequences to adult health and aging (3). Lastly, we recall Gärtner’s pioneering studies from 3 decades ago, which compared of twins derived from separate ova of inbred mice with those from artificially cleaved single ova. More than 70% of postnatal growth variance preexisted in oocytes at or before fertilization (101).

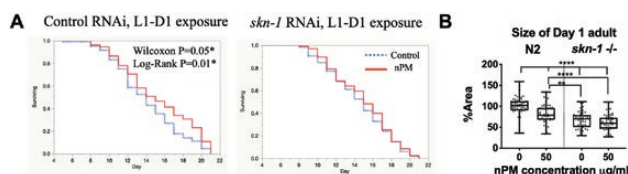


Figure 5. *Caenorhabditis elegans* impact of SKN-1 perturbation on AirPoll-nPM exposure during development. (A) Survival curves showing increased longevity from nPM exposure (hormesis) and its abrogation by *skn-1* knockdown. (B) Body size (area, arbitrary units) of adult day 1 wild-type (N2) and *skn-1(zu135)* mutant. Adapted from Haghani et al. (80). AirPoll = air pollution; CigS = cigarette smoke.

Concluding Perspectives

The search for individual determinants of health and longevity can be expanded to include environmental factors across the life span, from gametes to geronts.

Environmental interactions with genes over the lifetime ($G \times E \times T$) should consider interactions of the Exogenous and Endogenous domains of the Gero-Exposome, for example, adiposity from gestational exposure to CigS and AirPoll.

The Tripartite Phenotype of Aging includes cell heterogeneity that arises from developmental variations and variegated gene expression. The next phase of Systems Gerontology could include stochastic features of aging organ and cell data for modeling.

The frontier of stochastics in biogerontology can be explored with single-cell transcriptomes and ChIPseq.

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Conflict of Interest

None declared.

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