“Does sunscreen promote hypertension?” and other questions. Novel interactions between vitamin D and the renin-angiotensin axis. Focus on “The world pandemic of vitamin D deficiency could possibly be explained by cellular inflammatory response activity induced by the renin-angiotensin system”

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ASSOCIATIONS BETWEEN RENIN -angiotensin system (RAS) hyperactivity and chronic disease are widely recognized (13). Similar associations between vitamin D (VitD) hypoactivity and chronic disease are also well described (3). Emerging evidence suggests functional interaction between RAS and VitD effector pathways in disease pathogenesis and progression (13). The specific mechanisms whereby this may occur are incompletely understood and the subject of a review in this issue of the American Journal of Physiology-Cell Physiology (5).

Vitamin D receptors (VDRs) and VitD-metabolizing enzymes exhibit near-ubiquitous expression (2, 3), and ~3% of all mammalian genes, including renin genes, are directly or indirectly regulated by VitD (3). Corresponding biological effects extend well beyond calcium and bone homeostasis and include immunomodulation, cell cycle arrest, and cell differentiation (3). Like other nuclear hormone receptor ligands, genomic and nongenomic actions are known, and intracellular VDR localizes to multiple extranuclear compartments, including the cytosol, membranes, and mitochondria (8, 11). Evolutionarily, VitD effector pathways predate the appearance of vertebrates and skeletal development, with expression in plants, as well as animals (3). These pathways ostensibly evolved as control mechanisms over cellular calcium homeostasis and signaling (2, 3). The myriad biological effects of VitD, even those not traditionally associated with skeletal biology or systemic ion homeostasis, may derive from these central functions (2).

Functional RAS-like systems enjoy similarly broad, albeit nonidentical, phylogenetic and tissue expression (12), with effector orthologs identified in species as diverse as cartilaginous fish and humans (6). At nontoxic concentrations, VitD can attenuate RAS activation and associated morbidity (e.g., hypertension), in part, by directly repressing renin expression (3, 13). The converse relationship is poorly defined. The integrative suggestion that VitD and RAS signaling reciprocally interact to modulate proinflammatory contributions to disease (5) is a conceptually attractive extension of current dogma (Fig. 1) and, if validated, has potential clinical implications. Overlapping expression patterns are compatible with postulated counterregulatory functions in coexpressing cells and tissues (5). It is not known, however, whether such interactions occur in all coexpressing cells or are restricted to specific cell types or functions. Whether cells expressing intact VitD or RAS effector pathways, but not both, are functionally or developmentally distinguishable is also unknown. Until these features, their underlying mechanisms, and functional consequences are defined, it is difficult to address the utility of combinatorial RAS antagonism and VDR agonism in chronic conditions where causal roles for VitD and RAS signaling have been suggested (5).

Fig. 1. Proposed interaction between vitamin D (VitD) and renin-angiotensin system (RAS) effector pathway signaling (see Ref. 5). Reciprocal counteracting effects on common effectors or targets are thought to underlie phenotype development.
Broad overlapping distributions of RAS and VitD effector pathway expression (2, 3, 5, 6) and their functional complementarity are compatible with coevolutionary selection (5), although an unambiguous case for this notion is generally lacking. Simultaneous phylogenetic analysis of both pathways has been insufficiently detailed or systematic to fully address parallel or coupled selection. For example, it is widely accepted that birds arose from reptiles, which, in turn, arose from amphibians. It is therefore curious that amphibians and birds express VDRs, whereas their presumed reptilian intermediates do not (5). No corresponding gaps in RAS effector expression are observed (5, 6). Points of evolutionary divergence for individual pathway components are insufficiently delineated to provide an unambiguous framework for considering fundamental evolutionary issues, including operant selection pressures and mismatched pathway hypo- or hyper-activation that could contribute to associated pathobiology. The evolutionary discussion has largely focused on individual “proximate” (or mechanistic) issues, rather than “ultimate” (or evolutionary) factors.

In addition to endocrine, paracrine, and autocrine RAS activities, functional intracrine RAS units, some involving mitochondria, are well described (1). The VDR also localizes to most major intracellular compartments, including mitochondria (8, 11), but the regulation and functional relevance of mitochondrial compartmentalization are poorly understood. Mitochondrial targeting and translocation of nuclear receptors are well described (9), but direct mitochondrial gene transactivation by the VDR has not been demonstrated to our knowledge. Mitochondrial VDR localization is also ligand-independent and requires de novo protein synthesis (10). Despite suggestions that the mitochondrial permeability transition pore may constitute a VDR-conducting protein import pore (10), the physiological correlates of this apoptogenic pore have not been clearly defined, and functional data supporting such a contention are limited.

Mitochondrial RAS and VitD signaling integration has been proposed on the basis of the above-described findings and reported changes in mitochondria-associated VDR and angiotensin AT1 receptor mRNA abundance following VDR agonism (7). The functional relevance and compartmental specificity of these changes in transcript abundance have not been directly demonstrated, and associated nonspecific ultrastructural changes in mitochondria could reflect direct or indirect hormone actions. As such, these findings do not mechanistically inform the level(s) or form(s) of proposed effector cross talk. Although ligand-independent VDR targeting to mitochondria (10) does not exclude a role in integrating RAS and VitD signals, it is also not immediately suggestive of such a relationship. These findings are particularly interesting, given the fact that VitD and VDR functions do not always overlap (3). However, if mitochondrial VitD-RAS cross talk does occur as suggested (5), interactions via other, better-established mechanisms also remain likely (13), and it will be incumbent on future investigations to address the relative contributions of coexisting mechanisms.

Hypertension prevalence increases at higher geographic latitudes and ostensibly correlates with reduced overall solar exposure (4). Other factors are likely involved, and it does not follow that sunscreen or other means of reducing effective solar exposure meaningfully contribute to hypertension. Nonetheless, there is compelling evidence that VitD attenuates RAS activation and associated sequelae (13). The converse relationship is ill-defined. To address reciprocal counterregulatory VitD-RAS interactions, better models are needed to address the mechanistic and functional specificity of shared and unique effectors associated with RAS and VitD target processes and/or tissues. In principle, these interactions may occur at multiple nonexclusive levels via direct and indirect mechanisms. They can also occur systemically or be locally restricted. It is therefore relevant to ask the following questions: Do RAS and VitD pathways converge to regulate expression of the same genes in the same cells (Fig. 1)? Where both genomic and nongenomic mechanisms exist, is there evidence to suggest that one effector pathway is dominant over the other? The answers to these questions are needed to advance this line of inquiry. Taken together, the mechanistic and functional integration of VitD and RAS signaling remains an underexplored, but fundamentally important, area to be addressed by systems biology and cell physiology.

GRANTS
This work was supported, in part, by the Flight Attendant Medical Research Institute (M. A. Crane-Godreau).

AUTHOR CONTRIBUTIONS
R.B.R. and M.A.C-G. prepared the figure, drafted the manuscript, edited and revised the manuscript, and approved the final version of the manuscript.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

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