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# Ethanolamine: A novel anti-aging agent

Patrick Rockenfeller<sup>1,\*</sup>, Didac Carmona-Gutierrez<sup>1</sup>, Federico Pietrocola<sup>2,3,4</sup>, Guido Kroemer<sup>2,3,4,5,6,7</sup>, and Frank Madeo<sup>1,8,\*</sup>

<sup>1</sup>Institute of Molecular Biosciences; NAWI Graz, University of Graz; Graz, Austria; <sup>2</sup>Equipe 11 labellisée par la Ligue contre le Cancer; Centre de Recherche des Cordeliers; Paris, France; <sup>3</sup>Cell Biology and Metabolomics Platforms; Gustave Roussy Comprehensive Cancer Center; Villejuif, France; <sup>4</sup>INSERM; U1138; Paris, France; <sup>5</sup>Université Paris Descartes; Sorbonne Paris Cité; Paris, France; <sup>6</sup>Université Pierre et Marie Curie, Paris, France; <sup>7</sup>Pôle de Biologie; Hôpital Européen Georges Pompidou; AP-HP; Paris, France; <sup>8</sup>BioTechMed-Graz; Graz, Austria

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Ethanolamine (Etn) is a naturally occurring aminoalcohol necessary for synthesis of the phospholipid phosphatidylethanolamine (PE), a major component of biological membranes. We recently reported that Etn treatment increases cellular PE levels, thereby inducing cytoprotective autophagy and protecting against aging across species.

Phosphatidylethanolamine (PE) is a central intermediate of lipid metabolism and a major component of biological membranes.<sup>1,2</sup> Within cellular membranes, PE not only serves as a structural phospholipid but also regulates the tethering of proteins and fusion processes.<sup>3</sup> PE orchestrates the interaction with membrane-associated proteins, both by directly ingrain proteins into membranes and as a precursor for glycosylphosphatidylinositol (GPI) anchors.<sup>3,4</sup> Importantly, PE is also directly involved in the process of macroautophagy (hereafter termed autophagy), a lysosome-dependent cellular recycling mechanism<sup>5</sup> that protects cells against lethal stress and extends longevity in model organisms.<sup>6</sup> During autophagy, double-membraned structures that are highly abundant in PE engulf superfluous, supernumerary, or dysfunctional macromolecules or organelles contained in the cytoplasm, forming vesicles (autophagosomes). These autophagosomes then fuse with lysosomes to generate autophagolysosomes in which the luminal cargo is degraded. Importantly, PE serves as a lipid anchor for a protein essential for several steps of the autophagic process that is

called autophagy related protein 8 (Atg8) in yeast or microtubule-associated protein 1A/1B-light chain 3 (LC3) in mammalian cells.<sup>7</sup> The importance of LC3 (or Atg8) in the autophagic process is reflected by the fact that many assays designed to measure autophagy rely on quantitation of the conjugation of LC3 to PE. This lipidation step increases the electrophoretic mobility of LC3 (which can be measured by immunoblot analysis) and causes its redistribution from a diffuse cytosolic pattern to so-called autophagic puncta (which can be visualized by immunofluorescence or by tagging LC3 with green fluorescent protein).

Given the widespread functions of PE as a precursor of several biosynthetic pathways, there is high demand for this metabolite (Fig. 1). A common PE pool feeds into all major cellular PE-consuming pathways, thus resulting in competition for PE between pathways.<sup>4</sup> As we have recently shown, this limitation can be overcome by genetic or pharmacological interventions. Overexpression of yeast phosphatidylserine decarboxylase 1 (Psd1), which catalyzes the step from phosphatidylserine to PE,

increased the levels of intracellular PE. Similarly, external administration of ethanolamine (Etn), a precursor of PE (Fig. 1) can increase the abundance of intracellular PE.<sup>8</sup> Supporting a crucial regulatory role for PE in autophagy, we observed that both external supply of PE and an increase in its internal generation similarly increased autophagic flux.<sup>8</sup> Stimulation of autophagy by PE could efficiently protect cells from necrotic or apoptotic cell death.<sup>6,9</sup> This is an important finding because unwarranted cell death may contribute to several age-related diseases including stroke, atherosclerosis, and cardiovascular disease, or neurodegenerative disorders such as Alzheimer's, Parkinson's, or Huntington's disease. Importantly, pharmacological Etn treatment extended the lifespan of yeast and fruit flies, as well as cultured mammalian cells,<sup>8</sup> underlining the potential of Etn as a potent autophagy and longevity drug.

Given its properties as a detergent and emulsifier, Etn is widely used in cosmetic, lifestyle, and household products such as hair colors, bleaches, washing powders, disinfectants, kitchen

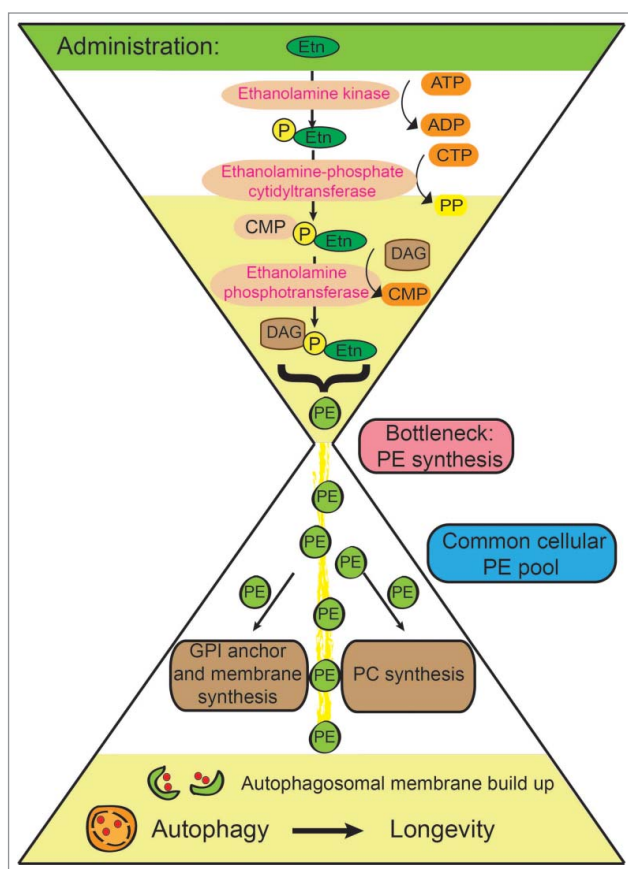
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\*Correspondence to: Patrick Rockenfeller; Email: patrick.rockenfeller@uni-graz.at, Frank Madeo; Email: frank.madeo@uni-graz.at

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**Figure 1.** The 'PE hourglass'. Simplified schematic of the conversion of ethanolamine (Etn) into phosphatidylethanolamine (PE) and its downstream products. Alternative pathways for PE production were omitted for clarity. PE synthesis is rate limiting because newly synthesized PE feeds into a common cellular PE pool, which is used for diverse cellular processes including glycosylphosphatidylinositol (GPI) anchor, membrane, and phosphatidylcholine (PC) synthesis as well as the generation of autophagic membranes. ADP, adenosine diphosphate; ATP, adenosine triphosphate; CMP, cytosine monophosphate; Etn, ethanolamine; CTP, cytosine triphosphate; DAG, diacylglycerol; P, phosphate; PE, phosphatidylethanolamine; PP, pyrophosphate.

cleaners, shampoos, and soaps. Thus, its toxicologic profile as an external agent

that may irritate the skin and mucosa is well studied. However, it remains to be

determined whether Etn can be used internally within the scope of increasing organismal PE levels, thereby stimulating autophagy and possibly conferring health benefits.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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