FE(II) AS AN ANCESTRAL COFACTOR FOR NUCLEIC ACID PROCESSING ENZYMES. Jessica C. Bowman, C. Denise Okafor, Kathryn A. Lanier, Anton S. Petrov, Shreyas S. Athavale, Nicholas V. Hud and Loren Dean Williams, School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332-0400.

Introduction: For the first two billion years of life on earth, biopolymers inhabited anoxic environments with abundant and benign Fe^{2+}. The geologic record indicates that early oceans contained vast quantities of soluble Fe^{2+}. Before the GOE, the reducing atmosphere would have attenuated Fe^{2+}-mediated oxidative processes such as Fenton chemistry [1, 2].

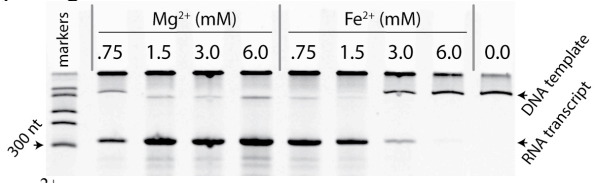
The GOE precipitated global shifts in biochemistry and microbiology, eventually producing the modern condition of iron scarcity and iron-mediated oxidative damage to biological systems [3]. It has been shown that the GOE drove substitution of copper, zinc, manganese and other metals for iron in protein enzymes [4-11] as well as tight cellular regulation of iron locations and concentrations [12]. The ubiquity of iron in extant biological systems emphasizes this element's catalytic utility and significance through evolutionary history.

We hypothesize that Fe^{2+} was a cofactor for nucleic acids and proteins during the origins of life when iron was abundant, and was substantially replaced by Mg^{2+} during the GOE. For RNAs, we observe that replacement of Mg^{2+} by Fe^{2+} *in vitro* improves and expands functional capabilities, enabling redox-activity. The nucleic acid processing proteins ligase and polymerases use Mg^{2+} to catalyze formation of the phophodiester bond joining adjacent nucleotides. In a generally accepted mechanism, Mg^{2+} cations stabilitize the 5' phosphate(s) of an incoming nucleotide and activate the 3' hydroxyl of an existing nucleic acid polymer for nucleophilic attack [13-19], facilitating subsequent bond formation.

We present evidence to suggest that Fe^{2+} was an ancestral cofactor for protein-based enzymes that process nucleic acids.

Model and Hypothesis: The GOE drove $Fe^{2+} \rightarrow Mg^{2+}$ substitutions in essential nucleic acid processing enzymes.

Results: Iron was substituted for Mg^{2+} in ligase and polymerase reactions performed under anoxic conditions. We demonstrate by experiment and supporting calculations that Fe^{2+} can indeed substitute for



Mg^{2+} in the catalytic function of these enzymes *in vitro*.

We propose that the rise of O_2 on Earth drove a Fe^{2+} to Mg^{2+} substitution in proteins as well as nucleic acids [20, 21], a hypothesis consistent with a general model in which some modern biochemical systems retain latent abilities to revert to primordial Fe^{2+}-based states under pre-GOE conditions.

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