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Heterogeneity to Homogeneity: Synthesis, base pairing and ligation studies of 4',3'-XyluloNA/RNA and TNA/RNA chimeric sequences

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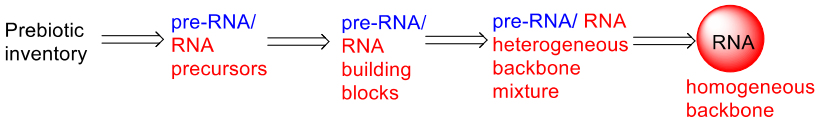

The "RNA world" hypothesis postulates an important role of RNA in the origin of life.[1] However, the difficulties associated with the synthesis of ribonucleoside and its polymerization under potential prebiotic condition[2] led to the assumption that RNA arose from a simpler "pre-RNA" polymer.[3] But this hypothesis raises another question – how did or could the transition from "pre-RNA" to "RNA" happen? [4] The progress from a homogeneous "pre-RNA world" to a homogeneous "RNA world" is contingent upon keeping their respective chemistries spatially separated.[4] However, based on the reality of "clutter" of prebiotic chemistry,[3] we herein present an alternate model which starts, not with homogeneous-backbone systems, but rather with mixtures of heterogeneous-backbones of a chimeric "pre-RNA/RNA".[4]

The formose reaction[5] and glyoxalate scenario[6] suggests the presence of pentulose sugars apart from the pentose sugars, on prebiotic earth. In addition, borate mediated formose reaction demonstrated the formation of threose,[7] and the reaction of glycolaldehyde with cyanamide also led to threose nucleic acid (TNA) and RNA nucleoside precursors[8]. Based on the prebiotic availability of a mixture of sugar precursors, we have synthesized and characterized two model chimeric nucleic acid sequences with sugar-backbone heterogeneity, containing a mixture of (4'→3')-L-xylulose(X^y)-NA with RNA, and (3'→2')-L-threose(T)-NA with RNA. The two chimeric X^yNA-RNA and TNA-RNA systems were found to exhibit unique base-pairing preferences suggesting that heterogeneous-backbone chimeric oligonucleotide systems (e.g. TNA-RNA) may transition to a homogeneous-backbone system (RNA). As a proof-of-principle, heterogeneous chimeric templates were found to mediate the non-enzymatic ligation of homogeneous-backbone oligonucleotides demonstrating a plausible constructive role for backbone-heterogeneity[4] in enabling the handover from chimeric "pre-RNA/RNA world" to a homogeneous "RNA world".

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