Iron: Primordial Cofactor for Biochemistry

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1
00:00:00,820 --> 00:00:08,980
[Music]

2
00:00:16,340 --> 00:00:12,499
all right so today I talk to you guys

3
00:00:17,750 --> 00:00:16,350
about some recent experiments we've done

4
00:00:20,779 --> 00:00:17,760
in the Williams lab that have really

5
00:00:23,029 --> 00:00:20,789
expanded the biochemical role for

6
00:00:25,160 --> 00:00:23,039
ferrous iron as a cofactor in

7
00:00:29,599 --> 00:00:25,170
biochemistry and sort of what that means

8
00:00:32,569 --> 00:00:29,609
for the origin of life so as many in

9
00:00:34,430 --> 00:00:32,579
this room I'm sure where life originated

10
00:00:36,620 --> 00:00:34,440
like volved on a very different earth

11
00:00:39,590 --> 00:00:36,630
than the one we know today we know and

12
00:00:41,590 --> 00:00:39,600
love in fact it was totally anoxic for

13
00:00:45,319 --> 00:00:41,600

at least about half the earth history

14
00:00:47,840 --> 00:00:45,329
with oxygen approaching modern levels

15
00:00:50,779 --> 00:00:47,850
only about half a million years ago and

16
00:00:54,080 --> 00:00:50,789
so what that allowed for was the buildup

17
00:00:57,260 --> 00:00:54,090
in persistence of very high amount of

18
00:00:59,689 --> 00:00:57,270
ferrous iron iron to relative to today

19
00:01:01,250 --> 00:00:59,699
and so life evolved you know between

20
00:01:03,500 --> 00:01:01,260
four and three billion years ago and

21
00:01:05,719 --> 00:01:03,510
then preceding that we had major your

22
00:01:09,109 --> 00:01:05,729
major biochemical functions and systems

23
00:01:11,480 --> 00:01:09,119
and so my adviser likes to say that that

24
00:01:13,789 --> 00:01:11,490
life life of evolved behind an iron

25
00:01:16,550 --> 00:01:13,799
curtain and so we can think of you know

26
00:01:18,200 --> 00:01:16,560
sort of what that means for the origin

27
00:01:19,700 --> 00:01:18,210
of life and how that affected the origin

28
00:01:22,330 --> 00:01:19,710
of life and so when I when I talk about

29
00:01:24,560 --> 00:01:22,340
sort of the central biochemical systems

30
00:01:26,719 --> 00:01:24,570
this was already brought up by our

31
00:01:28,789 --> 00:01:26,729
plenary speaker but sort of the central

32
00:01:31,100 --> 00:01:28,799
dogma of molecular G so the replication

33
00:01:34,249 --> 00:01:31,110
of DNA is transcription into RNA and

34
00:01:37,399 --> 00:01:34,259
then RNA subsequent translation into

35
00:01:39,590 --> 00:01:37,409
protein and so why why that would be

36
00:01:41,330 --> 00:01:39,600
important for thinking about you know

37
00:01:43,490 --> 00:01:41,340
what the cation content of the

38
00:01:45,679 --> 00:01:43,500

environment these were being designed or

39
00:01:48,850 --> 00:01:45,689
evolved in is that all these are totally

40
00:01:54,020 --> 00:01:48,860
dependent on on developmental cations in

41
00:01:58,160 --> 00:01:54,030
the the two first steps they're required

42
00:02:00,410 --> 00:01:58,170
for sort of structuring the the the

43
00:02:03,469 --> 00:02:00,420
nucleic acid in the binding site as well

44
00:02:06,440 --> 00:02:03,479
as a catalytic function of facilitating

45
00:02:09,440 --> 00:02:06,450
the the growing new nascent nucleic acid

46
00:02:11,930 --> 00:02:09,450
and then just a whole slew of structural

47
00:02:12,440 --> 00:02:11,940
and functional roles in translation and

48
00:02:14,420 --> 00:02:12,450
so

49
00:02:16,010 --> 00:02:14,430
what we think of now or at least what

50
00:02:17,720 --> 00:02:16,020
biochemist and buy organic chemists

51
00:02:20,059 --> 00:02:17,730
think of now mediating these functions

52
00:02:22,070 --> 00:02:20,069
is all magnesium it's all magnesium

53
00:02:24,500 --> 00:02:22,080
doing this stuff and so just oozing as

54
00:02:26,210 --> 00:02:24,510
an example I'm sure most of you we're

55
00:02:28,940 --> 00:02:26,220
solving in this room with setup PCR

56
00:02:30,620 --> 00:02:28,950
reactions so this is just a DNA

57
00:02:32,330 --> 00:02:30,630
replication reaction that you just use

58
00:02:35,449 --> 00:02:32,340
to amplify a bunch of DNA so you can

59
00:02:36,620 --> 00:02:35,459
work with it downstream and so in that

60
00:02:38,470 --> 00:02:36,630
sort of reaction you know you have a

61
00:02:41,030 --> 00:02:38,480
template DNA you have primers

62
00:02:43,309 --> 00:02:41,040
nucleotides your polymerase enzyme and a

63
00:02:45,860 --> 00:02:43,319

buffer and so you know what's really in

64
00:02:47,600 --> 00:02:45,870
that buffer besides you know any B or

65
00:02:50,000 --> 00:02:47,610
similar companies magic mix of things

66
00:02:51,559 --> 00:02:50,010
that make it go so well well one of one

67
00:02:53,930 --> 00:02:51,569
of the major components of that buffer

68
00:02:57,229 --> 00:02:53,940
is magnesium and that again is because

69
00:02:59,720 --> 00:02:57,239
it is so these enzymes are so dependent

70
00:03:02,000 --> 00:02:59,730
on magnesium and so you can say you can

71
00:03:04,069 --> 00:03:02,010
look at in vitro transcription reactions

72
00:03:08,210 --> 00:03:04,079
or translation kits and see the same

73
00:03:10,250 --> 00:03:08,220
exact thing and so again going back to

74
00:03:12,020 --> 00:03:10,260
thinkable then why is and why would I

75
00:03:13,580 --> 00:03:12,030
earn be important well we've done a lot

76
00:03:16,520 --> 00:03:13,590
of work in the Williams lab to sort of

77
00:03:19,009 --> 00:03:16,530
make build the case that that iron is is

78
00:03:21,110 --> 00:03:19,019
possibly interchangeable with magnesium

79
00:03:23,210 --> 00:03:21,120
in these systems and ink and can

80
00:03:25,509 --> 00:03:23,220
facilitate a lot of the same roles so

81
00:03:28,039 --> 00:03:25,519
here we just have an in silicon model

82
00:03:31,460 --> 00:03:28,049
interaction with either a magnesium or

83
00:03:33,199 --> 00:03:31,470
an iron in an RNA molecule found the

84
00:03:36,050 --> 00:03:33,209
phosphate backbone and you can just see

85
00:03:38,300 --> 00:03:36,060
how incredibly conserved the geometry

86
00:03:41,710 --> 00:03:38,310
and the bond length is if you take that

87
00:03:44,599 --> 00:03:41,720
out that magnesium and put an iron in

88
00:03:46,699 --> 00:03:44,609

we've also shown that iron can mediate

89
00:03:50,590 --> 00:03:46,709
the folding of nucleic acids and so this

90
00:03:52,789 --> 00:03:50,600
is just this is the 23 s large subunit

91
00:03:54,949 --> 00:03:52,799
ribosomal RNA and what we're looking at

92
00:03:58,970 --> 00:03:54,959
here is just sort of a heat map of

93
00:04:02,300 --> 00:03:58,980
places where structural changes have

94
00:04:04,849 --> 00:04:02,310
been induced on this molecule with the

95
00:04:07,699 --> 00:04:04,859
addition of either magnesium or iron and

96
00:04:10,580 --> 00:04:07,709
what we can see is that the structural

97
00:04:12,440 --> 00:04:10,590
changes that magnesium induces are

98
00:04:14,839 --> 00:04:12,450
broadly similar to the structural

99
00:04:16,400 --> 00:04:14,849
changes that iron is inducing so places

100
00:04:18,020 --> 00:04:16,410
where it's it's red and with the

101
00:04:19,750 --> 00:04:18,030
magnesium map it's red in the iron map

102
00:04:22,900 --> 00:04:19,760
places where it's blue and the magnesia

103
00:04:24,820 --> 00:04:22,910
that it's blue in the iron map and so

104
00:04:27,070 --> 00:04:24,830
you know thinking about all this an

105
00:04:28,480 --> 00:04:27,080
impossibly iron you know really looks

106
00:04:30,520 --> 00:04:28,490
like in substitute we wanted to go in

107
00:04:33,760 --> 00:04:30,530
and then see if it could be a functional

108
00:04:36,400 --> 00:04:33,770
substitute and so we first looked at the

109
00:04:38,590 --> 00:04:36,410
first step of the central dogma so DNA

110
00:04:41,530 --> 00:04:38,600
replication this is just a gel of a PCR

111
00:04:42,970 --> 00:04:41,540
reaction on as you can as we can see as

112
00:04:44,650 --> 00:04:42,980
you go through more cycles of DNA

113
00:04:46,420 --> 00:04:44,660

replication that reaction you get more

114
00:04:49,690 --> 00:04:46,430
of your product DNA being produced and

115
00:04:52,000 --> 00:04:49,700
by around cycle twelve to sixteen you

116
00:04:54,070 --> 00:04:52,010
have plenty of of your product being

117
00:04:56,770 --> 00:04:54,080
produced and you can see on the gel when

118
00:04:59,200 --> 00:04:56,780
we swapped out the magnesium for iron we

119
00:05:01,570 --> 00:04:59,210
basically got the exact same gel so that

120
00:05:04,210 --> 00:05:01,580
was that was pretty cool you know irons

121
00:05:06,940 --> 00:05:04,220
working in this reaction so now we went

122
00:05:09,010 --> 00:05:06,950
to the next step and we used in vitro

123
00:05:12,990 --> 00:05:09,020
transcription react kit that you would

124
00:05:16,180 --> 00:05:13,000
just buy from for many old supplier and

125
00:05:18,760 --> 00:05:16,190
we basically transcribed a three a three

126
00:05:20,320 --> 00:05:18,770
hundred nucleotide template into RNA

127
00:05:21,400 --> 00:05:20,330
that we could then see on the gel here

128
00:05:23,380 --> 00:05:21,410
and we did this over a range of

129
00:05:26,380 --> 00:05:23,390
concentrations and we can see that with

130
00:05:29,290 --> 00:05:26,390
the magnesium transcription works best

131
00:05:30,970 --> 00:05:29,300
in the low millimolar range here then

132
00:05:33,400 --> 00:05:30,980
when we swapped out my museum for the

133
00:05:35,140 --> 00:05:33,410
iron what was really interesting we saw

134
00:05:37,960 --> 00:05:35,150
that the optimum for iron is about

135
00:05:40,240 --> 00:05:37,970
almost an order of magnitude lower so

136
00:05:43,150 --> 00:05:40,250
iron is a supporting transcription as

137
00:05:47,260 --> 00:05:43,160
well as magnesium at an order of

138
00:05:49,300 --> 00:05:47,270

magnitude lower in in addition to that

139
00:05:50,620 --> 00:05:49,310
on the other side it's actually

140
00:05:52,720 --> 00:05:50,630
inhibitory towards the higher

141
00:05:54,970 --> 00:05:52,730
concentrations and by six millimolar you

142
00:05:56,110 --> 00:05:54,980
don't really see any transcript being

143
00:05:58,120 --> 00:05:56,120
produced with the iron so that was

144
00:06:00,460 --> 00:05:58,130
really interesting we're not totally

145
00:06:03,910 --> 00:06:00,470
sure why it's inhibitory at the higher

146
00:06:05,590 --> 00:06:03,920
concentrations and so that's something

147
00:06:09,370 --> 00:06:05,600
we're working towards looking at right

148
00:06:11,080 --> 00:06:09,380
now so the first two steps look to be

149
00:06:13,560 --> 00:06:11,090
good we can substitute the magnesium for

150
00:06:16,210 --> 00:06:13,570
the iron they only want the last step

151
00:06:19,660 --> 00:06:16,220
translation which is arguably you know

152
00:06:21,820 --> 00:06:19,670
by far the most intricate at least

153
00:06:25,480 --> 00:06:21,830
respect to with respect to what the

154
00:06:28,150 --> 00:06:25,490
cations are doing in this process and so

155
00:06:29,530 --> 00:06:28,160
here we just have a plot with our

156
00:06:31,180 --> 00:06:29,540
protein production we just use the

157
00:06:33,280 --> 00:06:31,190
activity of the protein produced as a

158
00:06:35,320 --> 00:06:33,290
proxy for how much there is

159
00:06:37,840 --> 00:06:35,330
and we also measured this reaction of a

160
00:06:39,550 --> 00:06:37,850
range of concentrations and so when we

161
00:06:41,190 --> 00:06:39,560
look at the magnesium this is really

162
00:06:44,800 --> 00:06:41,200
what other people found a very

163
00:06:47,670 --> 00:06:44,810

concentration dependent with a a maxima

164
00:06:50,230 --> 00:06:47,680
and activity around 9 to 10 millimolar

165
00:06:53,700 --> 00:06:50,240
we swapped out majority magnesium for

166
00:06:56,350 --> 00:06:53,710
iron we saw that it's definitely

167
00:06:58,030 --> 00:06:56,360
facilitating supporting translation I'll

168
00:06:59,950 --> 00:06:58,040
beat it a little bit lower rates so

169
00:07:02,130 --> 00:06:59,960
unlike the first two steps that look

170
00:07:06,520 --> 00:07:02,140
like it's just it's going just as well

171
00:07:08,560 --> 00:07:06,530
but again the concentration dependence

172
00:07:13,510 --> 00:07:08,570
looks to be the same with the Maxima

173
00:07:14,980 --> 00:07:13,520
around 9 to 10 mil more so we really

174
00:07:17,230 --> 00:07:14,990
basically be able to go through each

175
00:07:19,300 --> 00:07:17,240
step of the central dogma and replace

176
00:07:21,400 --> 00:07:19,310
the divalent cation from and using the

177
00:07:23,110 --> 00:07:21,410
iron so we can sort of think boss about

178
00:07:25,840 --> 00:07:23,120
a new central dogma at least with

179
00:07:27,340 --> 00:07:25,850
respect to to the cation and we can even

180
00:07:29,410 --> 00:07:27,350
think about these other reactions that

181
00:07:31,600 --> 00:07:29,420
people sometimes including the central

182
00:07:33,730 --> 00:07:31,610
dogma RNA replication reverse

183
00:07:36,430 --> 00:07:33,740
transcription while we haven't tested

184
00:07:38,110 --> 00:07:36,440
these yet sort of posit whether or not

185
00:07:40,060 --> 00:07:38,120
iron can facilitate these and it's it's

186
00:07:42,540 --> 00:07:40,070
likely probably given that both of these

187
00:07:45,030 --> 00:07:42,550
processes are polymerase dependent like

188
00:07:48,580 --> 00:07:45,040

DNA replication and reverse

189
00:07:50,920 --> 00:07:48,590
transcription and so what does this

190
00:07:53,890 --> 00:07:50,930
really mean for the origin of life well

191
00:07:55,200 --> 00:07:53,900
thinking back about how you know these

192
00:07:59,080 --> 00:07:55,210
biochemical systems were designed

193
00:08:00,820 --> 00:07:59,090
evolved and then used in cells you know

194
00:08:04,270 --> 00:08:00,830
all in a Frisian environment for you

195
00:08:06,420 --> 00:08:04,280
know 2 to 3 billion years we can think

196
00:08:09,940 --> 00:08:06,430
of you know iron is sort of the OG

197
00:08:14,050 --> 00:08:09,950
cofactor for at least you know either

198
00:08:16,300 --> 00:08:14,060
totally iron or in together with with

199
00:08:20,430 --> 00:08:16,310
some magnesium and then but then the

200
00:08:24,550 --> 00:08:20,440
switch over to totally fully magnesium

201
00:08:27,730 --> 00:08:24,560
chemistry biochemistry is sort of more

202
00:08:30,070 --> 00:08:27,740
of a recent contingency plan if you will

203
00:08:31,390 --> 00:08:30,080
that life had to come up with once we

204
00:08:33,640 --> 00:08:31,400
approach you know half a million years

205
00:08:37,780 --> 00:08:33,650
ago and all of your hands started to to

206
00:08:39,880 --> 00:08:37,790
leave and so that's all I have

207
00:08:42,010 --> 00:08:39,890
I just like to thank both my labs both

208
00:08:44,050 --> 00:08:42,020
my advisers dr. Jen glass and yes and

209
00:08:47,550 --> 00:08:44,060
dr. Lauren Williams in chemistry and

210
00:08:51,930 --> 00:08:47,560
biochemistry in their respective labs

211
00:08:53,490 --> 00:08:51,940
funding sources as well as cornea tucky

212
00:08:56,550 --> 00:08:53,500
from nuuma Biolabs who is very helpful

213
00:09:12,120 --> 00:08:56,560

with logistical things so I'll take any

214
00:09:14,100 --> 00:09:12,130
questions maybe I missed it um did you

215
00:09:20,160 --> 00:09:14,110
happen to do any experiments where you

216
00:09:21,840 --> 00:09:20,170
use say 50/50 iron and magnesium just to

217
00:09:24,150 --> 00:09:21,850
like demonstrate that at range ya know

218
00:09:26,190 --> 00:09:24,160
the functional experiments we've done

219
00:09:28,970 --> 00:09:26,200
some experiments where he looted

220
00:09:31,410 --> 00:09:28,980
association with certain molecules

221
00:09:34,710 --> 00:09:31,420
select competition and it looks like the

222
00:09:36,210 --> 00:09:34,720
iron is binding stronger and that is a

223
00:09:38,340 --> 00:09:36,220
lot to do with the fact that iron just

224
00:09:40,800 --> 00:09:38,350
seems to be a better lewis acid and that

225
00:09:42,870 --> 00:09:40,810
also goes back to why the iron was

226
00:09:46,140 --> 00:09:42,880
looking like it was mediating

227
00:09:48,090 --> 00:09:46,150
transcription at lower concentrations so

228
00:09:49,680 --> 00:09:48,100
we would you expect if you put like a

229
00:09:53,220 --> 00:09:49,690
50/50 in this sort of thing and then