Nucleic Acids Chemistry beyond the Watson-Crick Double Helix (67): Effects of malignant alteration in cancer cells on the DNA G-quadruplexes and transcript mutations

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The DNA sequences with the potential to form G-quadruplexes locate in oncogenes or proto-oncogenes. We previously showed that the frequency of transcript mutations depends on the stability of the G-quadruplexes formed in the template DNAs.[1] The G-quadruplex formation is highly responsive to surrounding conditions, particularly K^+ concentration. Malignant cancer cells have a much lower K^+ concentration than normal cells because of overexpression of a K^+ channel; thus, G-quadruplexes may be unstable in cancer cells.

Here, we investigated physicochemically how changes of intracellular chemical environments influence G-quadruplex formation and transcription during tumor progression in cells. We designed template DNAs with a G-quadruplex (D1, D2, D3, or D4) and without G-quadruplex (Linear). Thermodynamic analysis showed that the G-quadruplexes in D2 and D4 were very stable. The effect of the G-quadruplex stability on the production of run-off transcripts was also estimated. In a normal cell (NIH3T3 cell), the transcription efficiency inversely correlated with G-quadruplex stability (Figure 1a). Interestingly, higher transcript levels were produced from templates with G-quadruplex-forming potential in the Ras-transformed cell with highly metastatic properties than in the normal cell (Figure 1b). These results suggest that in normal cell, K^+ ions attenuate the transcription of certain oncogenes by stabilizing G-quadruplex structures.[2] In our presentation, we will discuss how the stability of G-quadruplexes in cell is changed during tumor progression.

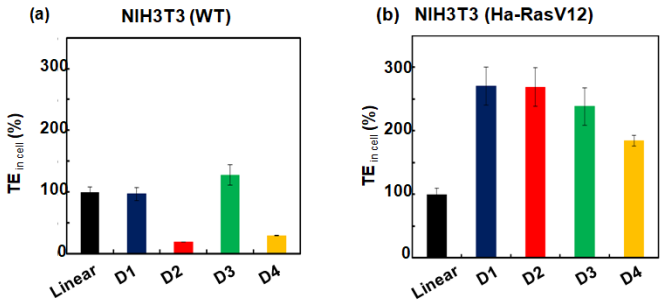

Figure 1. Effect of the G-quadruplex stability on the production of run-off transcripts (transcription efficiency in cell: $TE_{in\ cell}$). The $TE_{in\ cell}$ values from each template encoded on a plasmid in (a) NIH3T3 and (b) NIH3T3 (Ha-RasV12) cells. qRT-PCR was performed to quantify run-off transcripts.

1) H. Tateishi-Karimata, N. Isono, N. Sugimoto, *PLoS ONE.* **2014**, *9*, e90580

2) H. Tateishi-Karimata, K. Kawauchi, N. Sugimoto, *J. Am. Chem. Soc*. **2018**, *140*, 642.