第６回　疾患エピゲノムコアセンターセミナー

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Role of BLM and RECQL4 helicases to maintain nuclear and mitochondrial genome integrity

BLM and RECQL4 belongs to RecQ helicase family which is conserved across evolution. Mutations in these two tumour suppressors lead to Bloom Syndrome (BS) and Rothmund Thomson Syndrome (RTS). These autosomal recessive disorders are characterized by predisposition to cancers and abnormalities to multiple DNA metabolism processes. While BLM is a nuclear helicase having defined roles in homologous recombination (HR), RECQL4 localizes to the mitochondria and acts as an accessory protein to PolGA during mitochondrial replication.

We have recently found that the entry of RECQL4 helicase into the mitochondria is facilitated by RNF153/MARCH5/Mitol dependent ubiquitylation. This ubiquitylation at specific residues of RECQL4 enhances its turnover on the mitochondrial outer membrane, thereby acting as a negative regulator for its mitochondrial entry and during PolGA dependent mitochondrial replication. Consequently RTS mutants cannot undergo RNF153/MARCH5/Mitol dependent ubiquitylation and hence enters mitochondria with reduced efficiency.

Further we have recently shown that the recruitment of BLM to the annotated sites of double strand breaks in the genome is dependent on multiple parameters including ATM, MRN complex and RNF8 dependent BLM K63-linked ubiquitylation. Once recruited BLM can negatively regulate both HR and non-homologous end joining in a cell cycle dependent manner thereby maintaining genome integrity. The detailed mechanisms by which BLM and RECQL4 carry out the above functions will be discussed.

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本セミナーは医学履修課程特別セミナー等を兼ねています。
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