CONFÉRENCE DU CONSEIL SCIENTIFIQUE

Physiopathological DNA repair in immune and cancer cells

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DNA double-strand breaks (DSBs) are among the most dangerous forms of DNA damage, and their accurate repair is essential for preserving genome integrity and ensuring cell survival. Cells rely primarily on two pathways for repairing DSBs—homologous recombination (HR) and non-homologous end-joining (NHEJ). The selection between these pathways, known as DSB repair pathway choice, is a finely tuned process regulated by cell-cycle stage, chromatin context, and the availability of specific repair factors. DSB repair is also a cornerstone of adaptive immunity. B lymphocytes deliberately introduce DSBs to diversify their antigen receptor repertoire through V(D)J recombination and to alter immunoglobulin isotypes via class switch recombination—both of which rely on NHEJ. When canonical NHEJ or HR is compromised, cells can engage an alternative end-joining (alt-EJ) pathway, which is often error-prone and has been linked to structural genome alterations and tumorigenesis. Notably, cancers harboring BRCA1 or BRCA2 mutations depend heavily on such alternative pathways, creating therapeutic vulnerabilities to PARP and polymerase theta (Polθ) inhibition. In this seminar, I will discuss recent advances in understanding the molecular mechanisms that control DSB repair and pathway choice, highlighting how these processes maintain genome stability and how their deregulation contributes to immunodeficiency and cancer.

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