Stem cells guard tissue integrity by renewing the pool of differentiated cells, and must therefore be shielded from threats such as transposable elements or viruses. In that line, stem cells can largely resist viral infections, but they do so without deploying the antiviral pathways at play in differentiated cells. So, what guards the guardians? I recently discovered a stem cell-specific immune pathway, driven by a protein termed aviD (antiviral Dicer), which mounts an antiviral RNA interference (RNAi) response and thwarts RNA virus infection. This illustrates that stem cells implement specific defence mechanisms that are poorly understood, or unknown. My proposal aims at bridging the current knowledge gap in stem cell immunity. We will do so by investigating the role of the aviD pathway in vivo using an aviD knock-out mouse, as well as by unravelling the molecular regulation of the pathway (Aim 1). Stem cell’s demise can additionally be provoked by the expression of transposable elements.
Converging evidence suggests that aviD and the RNAi pathway may play a second defensive role in shielding uninfected stem cells from TE expression, which we will explore in Aim 2. Because cancer is characterised by a stemness transcriptional program, aviD may similarly control TEs in tumour cells. We will study aviD expression in various tumour models and assess its role in controlling TEs. This is of special interest because awakening TE expression in cancer is being leveraged by new therapeutical approaches in multiple malignancies. Similarly, we will explore if inhibiting aviD and the RNAi pathway could have an antitumour effect (Aim 2). Finally, I hypothesize that stem cells are protected by additional, unknown antiviral pathways, which we aim to identify and characterise using new genome-scale approaches (Aim 3). Overall, this proposal aims at unveiling new biology in stem cell immunity as well as developing clinical applications in the field of antitumour therapy.
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