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На правах рукописи

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Анализ противовирусного ответа NK-клеток: от классического до антиген-специфической памяти

Специальность: 1.5.3. Молекулярная биология

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DISSERTATION ABSTRACT

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General characteristics of the work

PhD thesis topic relevance. Natural Killer (NK) cells are critical components of the immune system, traditionally classified as innate lymphocytes that respond rapidly to virally infected or transformed cells without prior sensitization. They play a pivotal role in controlling viral infections, including widespread pathogens like human cytomegalovirus (hCMV) and Epstein–Barr virus (EBV), as well as emerging threats such as SARS-CoV-2 [Hatton et al., 2016; Masselli et al., 2020; Wu et al., 2013]. Viral infections pose significant public health challenges, for instance, EBV infects the majority of humans and can cause mononucleosis or contribute to cancers, while hCMV persists lifelong in most adults and can reactivate with serious consequences in immunocompromised individuals [Damania, Kenney, Raab-Traub, 2022; Kenneson, Cannon, 2007]. The recent COVID-19 pandemic caused by SARS-CoV-2 further highlights the need to understand antiviral immune defenses. NK cells serve as a first line of defense in these contexts, capable of directly lysing infected cells and secreting cytokines.

Notably, research in the past decade has uncovered that NK cells can exhibit adaptive features, such as antigen-specific memory-like responses, blurring the line between innate and adaptive immunity [Gumá et al., 2006; Paust, Andrian Von, 2011]. A well-documented example is hCMV, which drives the expansion of a specialized NK subset characterized by the activating receptor NKG2C along with maturation markers such as CD57 [Gumá et al., 2006; Wu et al., 2013]. These hCMV-associated adaptive NK cells can persist and respond more rapidly upon re-exposure to the virus. However, there is a significant knowledge gap in understanding adaptive-like NK cells in other viral infections.

Moreover, emerging evidence indicates that NK cell responses to certain viruses may depend on the personal combination of KIRs (Killer-cell Immunoglobulin-like Receptors) and their HLA class I ligands and even more on the peptides presented within HLA-I molecules [Chapel et al., 2017; Colantonio et al., 2011; Hansasuta et al., 2004; Naiyer et al., 2017; O'Connor et al., 2015; Rettman et al., 2020; Stewart-Jones et al., 2005], analogous to how T cells recognize specific peptide-MHC complexes. Given that KIR genes are highly polymorphic, and each NK cell clone expresses a subset of these receptors, the personalized HLA-KIR landscape is thought to shape the effectiveness of NK cells recognizing and remembering virus-infected cells. Understanding these complex interactions is highly relevant, as it can explain variability in infection outcomes between individuals.

The topic of this dissertation addresses how NK cells respond to viral infections such as hCMV, EBV, and SARS-CoV-2 ranging from innate to adaptive-like behavior. This research not only deepens fundamental knowledge of NK cell immunobiology but also holds promise for improving antiviral immune monitoring and immunotherapeutic approaches.

Research objectives. The main aim of this work is to investigate the adaptive antiviral properties of human NK cells by examining their responses across different viral infections and identifying mechanisms that underpin NK cell specificity and memory-like behavior.