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# The Natural Killer Cell

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**Abstract**

Natural Killer Cells (NK) are an important, but not readily discussed type of lymphocyte that occur in all primates. It has evolved as a regulator of tumor cell activity but has diverse functions in both cancer and the recognition of "self", which is especially important related to pregnancy. NK cells also have important implications in the understanding of the mechanics and control of parasitic diseases, including viral infections.

## Introduction

The "natural" activity of some heterogeneous immune preparations was noticed in the 1960's with experiments related to tumor cells. In the 1970's, the activity was better established [1,2]. Eventually the K562 chromium-based assay which selects for NK functional activity was developed. This led to visualization of isolated cells, which to this day is one of the most important in immunological history.

Natural Killer Cells (NK) are a type of large cytotoxic granular lymphocyte which are one of the types of immune cells that are part of the non-specific immune response in that they target pathogens types in general as opposed to specific antibody. They constitute a range of 5 % to 20 % of circulating lymphocytes [1]. They provide rapid response to virus and other intracellular pathogens. NK cells can react in a somewhat more rapid way as they do not require antibodies or MHC to react to normal cells which have been compromised by some pathogen or other stimulation such as allergen.

NK cells have the CD56 antigen on their surface and they lack CD3. They originate in the bone marrow as do B and T lymphocytes. NK cells also mature in the bone marrow, lymph nodes and other lymphoid tissue [3]. NK cells do not express T-cell antigen receptors but do express CD16 and CD57. NK cells are involved in self-tolerance and feedback so that they are continually stimulated. There is some evidence that NK cells are involved in immunologic memory and importantly involved in response to tumor cell activity.

NK cells can be classified as either CD56 "bright" or "dim", largely based on quantity in circulation. CD56 bright NK cells are found in bone marrow, liver and skin [4,5]. CD56 dim NK cells are found in the peripheral blood. CD56 dim cells will always have the CD16 receptor on the cell surface. SARS-CoV-2 patients are depleted in CD56 bright cells but will maintain a consistent level of the dim cell type, except in sever cases.

NK receptors are on the surface of the cell are differentiated based on their function. NK activation may be controlled by a "balance" between receptor stimulation, that is between those that active and those that inhibit [6]. If the signal that activates NK cells is more prevalent, then cell activation will be of greater prominence. Receptors that are involved in activation include CD16 which bind to IgG and are involved in antibody dependent cell mediated cytotoxicity. Receptors that are involved with inhibition include killer-cell immunoglobulin receptors that help to down regulate and thus inhibit NK cell killing activity.

## Role and Function of the NK cell

NK cells are by definition cytotoxic killer cells. They release proteases which are contained in small self-contained granules in the cytoplasm of the NK cell [7]. Pores or aqueous channels are formed in the intruder (pathogenic) cell though which proteases can enter the target. The best outcome is apoptosis of the target as both the infected cell and the virus or parasite is destroyed, which does not occur with target cell lysis. Defensins which are used by neutrophils to destroy bacterial cells directly may also be released by NK cells. This is another example of conservation in nature where a molecule is used by two different cell types for a similar aim.

NK cells are activated by a wide variety of cytokines including IL-2 and interferon. Gamma interferon that is secreted by NK cells has long been known to deactivate virus in a non-specific manner. Gamma interferon activates macrophages. The release of tumor necrosis factor by NK cells will interact with virus and bacteria directly.

Tumor cell control and destruction is one of the most important aspects of natural killer cell function. Part of the reason is that they are a function of non-specific immunity in that they can react to pathogenic threats quickly without the need for prior programing. They do not have cell receptors that are antigen specific. Other cell types require specific cell surface receptors to have an immune effect. Tumor cell presence followed by immune detection causes NK cells to activate with the subsequent release of cytokines. Cytokines are chemical messengers with their language being received at the cell receptor level. The cytokine release causes other aspects of the non-specific immune response to activate, such as T lymphocytes, macrophages, and neutrophils. This allows for the activation of T and B lymphocytes (and plasma cells) which are antigen specific.

Tumor cells do have the ability to evade NK interactions and thus destruction by shedding a decoy [8]. This decoy is a soluble ligand that

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interacts with NKG2D receptors which activates a false NK response. Thus, there is competition and confusion of a sorts at the receptor site. This is one of the prime mechanisms for the advancement of prostate cancer in men.

One other important function of NK cells occurs in pregnancy, and thus at least some suppression of the maternal immune response [9]. A subset of bright CD56 NK cells differ from peripheral NK cells in that they have a lower cytotoxic capability. They are the most prominent leukocyte cells type present *in utero*. It is thought that the reason for their reduced cytotoxic ability is due to a regulation of inhibitory receptors at the cell surface.

## Conclusion

Natural Killer cells and their activity remain something of a mystery in the biological world and have since their discovery. The therapeutic uses of activated NK cells are just now being understood. It is apparent that in cancer treatment if NK cells could undergo a directed mobilization, that certain cancers could be controlled to a greater degree. The best example could be prostate cancer where if the issue with ligand competition could be overcome, the disease would be better controlled.

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