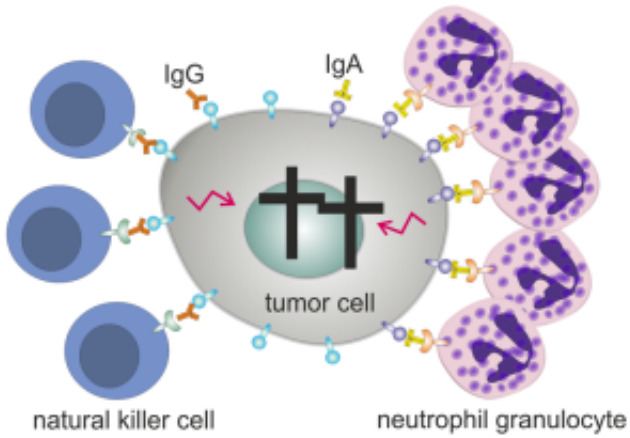
Combining different antibody flavors to improve cancer therapy

Our immune system is specialized at identifying ‘foreign intruders’ (pathogens) or virus-infected cells inside the human body. This can be achieved by antibodies (immunoglobulins) that circulate in our body and are able to bind targets with high specificity, such as bacteria. Antibody binding recruits different types of cells of the immune system, these are white blood cells such as neutrophil granulocytes or natural killer cells. These are specialized immune cell types that recognize antibodies bound to a target and subsequently initiate the elimination of these pathogens. Each effector cell type has its own specialized way of killing, for example by ‘eating’ the pathogen (phagocytosis) or by releasing toxic molecules that will kill the virus-infected cell.



Combining antibodies of different isotypes recruits both natural killer cells and neutrophil granulocytes for tumor killing, giving the tumor cell a ‘double-hit’.

By virtue of their specificity, antibodies can also specifically target tumor cells, and custom-made antibodies are nowadays being used in the treatment of cancer. For example, rituximab (Rituxan) is used for treating hematological cancers and trastuzumab (Herceptin) is used for treating certain types of breast cancer. Despite their demonstrated clinical efficacy, currently these antibodies are not effective enough to completely eliminate all tumor cells and to cure cancer. Therefore, improving the efficacy of anti-tumor antibodies would be of great benefit.

Based on their structure, antibodies in humans are classified into five different classes, called antibody ‘isotypes’. Each antibody isotype elicits different type of immune activation, providing a fine-tuning of the immune response. For instance, the IgA isotype is very efficient in recruiting a populous immune cell type in blood, called the neutrophil granulocytes. Currently, all antibodies in the clinic are of the IgG isotype.

We hypothesized that the combination of antibodies of different isotypes will lead to improved anti-tumor responses. In this study, we combined antibodies of the IgG isotype with antibodies of the IgA isotype. IgG antibodies mainly bind to natural killer cells, which then make close contact with the tumor cell and kill the tumor cell by releasing toxic molecules. IgA antibodies mainly activate to neutrophil granulocytes, which kill tumor cells by a distinct, less-known mechanism. Combining IgG and IgA antibodies would therefore result in the activation of two different immune cell types with distinct killing mechanisms. This could potentially increase the number of tumor cells that are killed.

We measured tumor cell killing by mixing human immune cells isolated from blood with tumor cells in the presence of the different antibodies. We found that the combination of IgG and IgA antibodies increases tumor cell killing when each isotype binds to a different target on the same tumor cell. If both antibodies bind to the same target, they compete for tumor cell binding and no increased killing was seen. We have also shown that mice with growing tumors can be treated with antibodies, and the combination of IgG and IgA antibodies inhibited tumor growth better than either isotype alone.

In conclusion, combining antibodies of different isotypes for the treatment of cancer is a new and promising approach to improve the anti-tumor responses. The combination of IgG and IgA isotypes recruits multiple types of immune cells (natural killer cells and neutrophil granulocytes) for tumor killing. Both effector cells will attempt to kill the tumor cell, and we believe that this combination will give a ‘double-hit’ (see Figure), increasing the effectiveness of killing. The combination of antibody isotypes might improve the outcome for cancer patients.

Publication

Simultaneous Targeting of Fc?Rs and Fc?RI Enhances Tumor Cell Killing.
Brandsma AM, Ten Broeke T, Nederend M,Meulenbroek LA, van Tetering G, Meyer S,Jansen JH, Beltrán Buitrago MA, Nagelkerke SQ, Németh I, Ubink R, Rouwendal G,Lohse S, Valerius T, Leusen JH, Boross P
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