Chapter 2
Therapeutically Used Targeted Antigens in Radioimmunotherapy

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Summary Many antigens have been tested as targets for radioimmunotherapy with intact antibodies. Some of the early used targets have been found to be of decreasing interest due to low expression, extensive shedding or other reasons. Others have been found more useful due to their accessibility, amount available in the tumours, or the biological properties of the target antigen. In this chapter some of the most used antigens and their characteristics are presented.

Introduction

An increasing number of promising antigens on malignant cells for monitoring malignant diseases have recently been reviewed [1]. Several of the seventy markers in that review have also been investigated for putative use in radioimmunotherapy, and this chapter will focus on some of them.

The ideal antigen for targeting should be readily accessible, expressed mainly within the targeted tissue, if possible, and should be present in substantial amounts. In the early history of targeting experiments, many of the antigens referred to as “tumour markers” were employed and even secreted products were used for targeting. Several of these early secreted targets have turned obsolete today and have disappeared or are used in very limited extent (HCG, α-fetoprotein) and instead new aspects on the nature of the target have come into focus. Some of the major antigens in use will be presented here.

The amount available and accessibility of the antigen in combination of biological properties affect the outcome of targeting. The selectivity in tissue expression is also of importance. Some antigens may be regarded as disease specific for certain malignancies, while others are expressed in different type of tumours. Such ubiquitously

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expressed targets may have advantages at clinical radioimmunotherapy in a wider perspective. Several of the most used antigens today are expressed in several tumour tissues as for example, CEA, TAG-72, HER2/neu, EGFR and VEGF. CEA is expressed in colorectal, gastric, pancreatic, non-small cell lung and breast carcinomas. TAG-72 is similarly expressed in colorectal, gastric, pancreatic, ovarian, endometrial, breast, non-small cell lung cancer and prostate carcinomas. The expression of EGFR and HER2 is described in detail in chapter 3 but shortly described also below. In order to minimize hematopoietic toxicity at radioimmunotherapy, it is a significant advantage if the tissue expression is limited to the diseased tissue.

One aspect, today more in focus than earlier, is the metabolic behaviour of the targeted antigen. Some antigens, possible to target, may reside on the plasma membranes of the malignant cells, but also extracellularly located target molecules within the tumour tissue may be considered, if they are present in significant amounts, e.g. in the tumour stroma or tumour vasculature.

Many useful membrane antigens exert their biological role by recycling between the plasma membrane of the host cell and the interior of the same cell, providing a mechanism for internalization of antibodies by the targeted malignant cell. At the same time, however, the antibody will be exposed to the intracellular degradation machinery, including proteolytic cleavages of the labelled compound, with possibilities to separate the nuclide from its carrier. This causes a consecutive and continuous transport out of the cell of the nuclide as a low molecular weight compound, which will be subjected to urinary excretion.

Improved cellular retention can be achieved by the use radioactive metals (e.g. $^{90}$Y or $^{177}$Lu) which, after degradation of the targeting agent, bind to intracellular structures or by the use of residualizing reagents during coupling of radioactive halogens (e.g. $^{131}$I or $^{211}$At) to the targeting agent, see chapter 8 for more details.

Some of the antigens widely used are released or even secreted from the tumours and this causes appearance of circulating intact or degraded products of these antigens within the vasculature, which may interfere with the efficiency in the targeting by consuming the labelled antibodies with subsequent degradation within the reticuloendothelial system. Both CEA and TAG-72 appear in blood in soluble form in low amounts, and will compromise binding to the tumour, while for example CD20 is an excellent target because it is neither shed, nor internalized and furthermore expressed by almost all B-cell tumours. The properties of this antigen may be one of the important reasons for the positive outcome when treating different types of lymphomas.

Some of the most used antigens are presented below.

**CEA**

When the concept of oncofoetal antigens was introduced, following the discovery of CEA by Gold and Freeman [2], CEA was soon to be the very first antigen to be used both as a tumour marker and as target for intervention in the treatment of malignant diseases [3, 4].