The Antibody Approach of Labeling Blood Cells

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Abstract

Although the science of blood cell labeling using monoclonal antibodies directed against specific cellular antigens is still in its early stages, considerable progress has recently been accomplished in this area. The monoclonal antibody approach offers the promise of greater selectivity and enhanced convenience since specific cell types can be labeled in vivo, thus eliminating the need for complex and damaging cell separation procedures. This article focuses on these developments with primary emphasis on antibody labeling of platelets and leukocytes. The advantages and the shortcomings of the recently reported techniques are critically assessed and evaluated.

Introduction

The important role of radiolabeled cellular blood elements in diagnostic nuclear medicine procedures is by now clearly well established. A variety of methods have been developed for labeling red blood cells (RBC), leukocytes (WBC) and platelets (P) with different radionuclides. Most techniques employ either ^{99m}Tc or ^{111}In, and a number of kit methods are now available for the in-vitro labeling of the above cell types with these radionuclides. Technetium-99m-RBC and ^{111}In-labeled WBC and platelets are now routinely used, for example in applications such as: cardiovascular blood pool imaging, detection of GI bleeding and hemangiomas, etc. (RBC); localization of inflammatory lesions (WBC); and for thrombus detection (P). In-vivo cell kinetics and survival in health and disease can be studied using longer-lived indium-111. Despite the proven usefulness of these methods in the clinical setting, however, research activity in the area of leukocyte and platelet labeling has continued with a view to developing newer and better techniques particularly those that overcome the serious disadvantage of cell separation before labeling.

The methodology for RBC labeling with ^{99m}Tc has matured to the point that available kit methods now assure highly reliable clinical data (Srivastava, 1990; Patrick,

1991). This is primarily a result of extensive mechanistic investigations of the uptake and binding of tin and technetium to various blood components which in turn have led to a clearer understanding of both in-vitro and in-vivo RBC labeling reactions (Srivastava, 1984). Non-specific cell labeling mechanisms such as the "pretinning" approach used for ^{99m}Tc-RBC when applied to leukocytes and platelets require prior cell separation (Srivastava, 1990). Cell separation methods are cumbersome, time consuming, and pose the likelihood of cell damage and thus a compromise in in-vivo cell function. Another non-specific technique involves the use of lipophilic chelates that are taken up into the cells by passive diffusion. This mechanism is utilized in the classical ^{111}In-oxine method (Desai, 1986), and more recently in ^{99m}Tc-HMPAO -labeling of both isolated leukocytes (Peters, 1986) and platelets. Following uptake into the cells, the radionuclide gets more strongly bound to intracellular components.

Specific cell labeling mechanisms include the in-vitro method for labeling leukocytes in whole blood based on the phagocytosis of tin-technetium colloids applicable to granulocytes and monocytes (Hanna, 1984; Srivastava, 1990), and the monoclonal antibody approach for labeling both leukocytes and platelets. Even though this latter approach is an evolving science that is still in its early stages, significant progress has been made during the last few years. These developments offer the promise to selectively label specific cell types in blood, in vitro or in vivo, thus overcoming the need for complex and damaging cell separation steps. Monoclonal antibodies directed against specific cellular antigens continue to be identified and developed (Buchegger, 1984; Bosslet, 1985; Coller, 1985; Thakur, 1987, 1988; McAfee, 1988a). A number of these have attracted considerable interest and are presently undergoing active investigation. This paper provides a brief review and assessment of the advantages and the shortcomings associated with these techniques that utilize cell-specific monoclonal antibodies, the focus being primarily on platelets and leukocytes.

Platelets

Since platelets play a crucial role in the formation of thrombi and other vascular lesions, much research has focused on the development of radiolabeled platelets for the scintigraphic localization of these lesions. Following adhesion to the damaged vessel wall, platelets undergo aggregation at these sites. These platelets also introduce biochemical changes that result in the release of various substances that accelerate fibrin production during thrombus formation. Platelets are not only important physiologic mediators of clot

formation but they also make up for a significant portion of the mass of the clots. Conventional ^{111}In-oxine labeled platelets, though useful for thrombus detection, are not ideal due to their high blood pool background. Since a monoclonal antibody directed against platelets would be expected to specifically bind to platelets in vivo, this approach has been investigated in detail for a number of years.

Coller et al (Coller, 1983) were the first to report the development of an antiplatelet antibody (7E3) directed against the fibrinogen receptor that consists of a glycoprotein IIb/IIIa complex on the platelet surface. Following further characterization of this antibody (Coller, 1985) studies were undertaken to develop chemical methods to label it with various radionuclides including ^{123}I, ^{131}I, ^{111}In, and ^{99m}Tc. Binding of the labeled antibody with platelets in whole blood was investigated and these labeled blood samples were evaluated for imaging experimental thrombi and vascular lesions in dogs (Srivastava, 1984; Oster, 1985; Srivastava, 1988). The antibody 7E3 belongs to the IgG1 subclass and inhibits ADP-induced platelet aggregation, as well as the ADP-induced binding of fibrinogen to platelets. There are 5 x 10^4 antibody binding sites per human platelet, and 7.5 x 10^4 binding sites per dog platelet. In vitro studies with human and dog platelets showed that: there is only one type of binding site; greater than 90% tracer antibody dose binds to human platelets; ~70% of tracer dose binds to dog platelets; there is negligible binding to other blood components; virtually all platelet-bound 7E3 becomes incorporated into thrombin produced clots; 10 μg antibody/ml blood causes total inhibition of platelet aggregation; and 0.5-1 μg antibody/ml blood did not produce any significant change in platelet function (Srivastava, 1984). The antibody was iodinated by reacting 100 μg of 7E3 with radioiodine (^{123}I, ^{131}I) at a molar ratio of iodine to antibody of ~0.5, in the presence of 5 μg Chloramine T as the oxidant. The Iodogen technique was equally effective. Labeling yields (following purification) were 30-80% depending upon the reaction conditions, and the specific activity ranged between 20-300 μCi/μg (for ^{123}I at an average of <0.5 iodine atoms per antibody molecule). Labeling with ^{111}In was accomplished after conjugating DTPA to the antibody using the cyclic anhydride method (Hnatowich, 1983). Labeling yields (using 100 μg antibody) were ~80% and the specific activity ranged between 10-40 μCi/μg at an average of 0.2 to 0.5 indium atoms per antibody molecule. Both iodine and indium labeled 7E3 displayed >90% binding specificity in the fibrinogen-coated bead assay (Coller, 1985).

Blood clearance in dogs of the 7E3-labeled platelets showed that the initial recovery was ~70%, very similar to indium-oxine-labeled platelets. Approximately 50% of injected activity remained in the blood at 30 min, dropped to 40-45% at ~60 min, and then

remained fairly constant up to 4 hr. Both iodine- and indium-7E3-labeled platelets showed a very similar blood clearance; plasma levels of ^{111}In were ~10% as opposed to ~5% for ^{123}I. Total urinary excretion at 4 hr was less than 2%. Arterial and venous clots were produced in dogs either by thrombin injection into vein segments, by transcatheter placement of a copper coil into blood vessels, or by electrocoagulation. One to 3 hr post-injection of the 7E3 labeled blood sample, clots in the lung as well as carotid thrombi were visualized well. Clot-to-blood ratios in various imaging experiments ranged between 5 and 35. Early and clear images of experimental arterial and venous thrombi in these areas were obtained in all experiments without the need for blood pool subtraction (Oster, 1985). Thrombus localization using ^{131}I-7E3-platelets was compared with the ^{111}In-oxine-platelet technique in the same animals (Ezekowitz, 1986). The venous thrombi were clearly imaged within 5-30 min with ^{131}I-7E3-platelets and in ~60 min with ^{111}In-oxine-platelets. The clot to blood ratios were approximately twice as high as with ^{111}In-oxine-platelets. Coronary thrombi were visible ex vivo but only one-third of the time in vivo at 3-4 hr after injection. Indium-111-oxine images at this time period were negative. It was concluded that more rapid blood clearance of 7E3-platelets, either through a manipulation of the degree of substitution of 7E3 on platelets, or through using antibody fragments, would be required for prompt and reproducible imaging of coronary thrombi (Ezekowitz, 1986; Srivastava, 1988).

Antibodies similar to 7E3 (glycoprotein IIb/IIIa antigen) have been investigated by other groups as well. In one study B 79.7 and B59.2 antibodies were labeled with ^{125}I and ^{111}In and shown to be effective for imaging experimental thrombi in animals (Thakur, 1987). The specific activities of ^{111}In and ^{125}I preparations averaged 5 and 2.4 Ci/μmol respectively. Scatchard analysis gave values of Kd for ^{111}In-B79.7 and ^{125}I-B79.7 as 83 x 10^{-9}M/L and 113 x 10^{-9}M/L respectively. MAb B59.2 reacted with canine platelets and at 50% antigen saturation, 49.5% of the ^{111}In-DTPA-B59.2 was bound to platelets. The thrombus to blood ratios averaged 15.8, 2 hr following injection of the labeled platelets. Clinical evaluation of these antibodies remains yet to be carried out. Other publications discuss results on ^{111}In and ^{99m}Tc-labeled P-256 antibody (whole IgG as well as Fab'$_2$) for imaging deep venous thrombi in patients (Peters, 1986a; Stuttle, 1988). In this study in six patients, DVT were imaged at 24 hr in three which had documented clots. Old thrombi were not detected. This is a current limitation of this approach since it images fresh clots where platelet adhesion is an active phenomenon. Prolonged circulation of labeled platelets is also a problem that needs to be resolved, as mentioned above.

Another antibody, 50H.19, that recognizes a low molecular weight tumor cell antigen

and also cross-reacts with human platelets recognizing three proteinase-sensitive low molecular weight antigens was evaluated for thrombus imaging (Som, 1986). A kit method was used to label 50H.19 fragments with ^{99m}Tc with an average of 97 ± 6% labeling yield. Binding to platelets in vitro or in vivo averaged around 60%. Approximately 50% of the radioactivity was cleared from the blood in 3-6 min and 18-24% was excreted in urine within 3 hr. Experimental thrombi in dogs in peripheral veins and arteries, pulmonary arteries and the right ventricle could be visualized 2-3 hr following injection. Blood pool subtraction or delayed imaging were not necessary. Detailed investigation in patients, yet to be carried out, will determine the eventual clinical effectiveness of ^{99m}Tc-50H.19 for thrombus imaging.

Another promising approach has been the development of antibodies specific for an external membrane protein of activated platelets (Palabrica, 1989). These "anti-activated platelet" monoclonal antibodies would seem to provide greater contrast for thrombus imaging since their binding to the normal circulating platelet pool can be expected to be small or negligible. A recent study in animals with ^{99m}Tc-labeled S12 (Chouraqui, 1991a) has suggested the potential usefulness of this agent for imaging coronary and other arterial thrombi in humans. In this study, 19 out of 20 femoral clots and 3 out of 3 coronary thrombi were visualized immediately after injection and remained positive until more than one hour. Blood clearance was biphasic with a t½ of the two components of 36 and 96 min respectively. The uptake of ^{99m}Tc-S12 by arterial thrombi, however, was found to decline rapidly with the age of the thrombus. This points to a diminished effectiveness (e.g., only ~35% for 48 hr old thrombi) of this technique for in vivo imaging of aged thrombi (Chouraqui, 1991).

A number of antifibrin antibodies have been found to be useful for imaging fresh as well as aged thrombi with a varying degree of effectiveness (Knight, 1988; McAfee, 1988). A discussion of these systems is beyond the scope of this paper since the emphasis is primarily on antibodies that recognize and label cellular antigens.

Leukocytes

Even though studies involving anti-leukocyte antibodies are still preliminary, some very promising results have been reported with the use of at least four antigranulocyte antibodies for the localization of abscesses and other inflammatory lesions (Table 1). The first report was by Locher et al (Locher, 1986) who presented data on imaging abscesses in

humans with an ^{123}I labeled anti-CEA MAb 47. This antibody was identified and developed by Mach's group in 1984 (Buchegger, 1984). The antibody is directed against a non-specific cross-reacting antigen (NCA 95) on the granulocyte surface, expressed particularly during the final stages of the development of these cells. Undifferentiated and rapidly proliferating early granulopoeitic cells do not bind the antibody. The only cross reaction was observed from CEA producing tumors. The antibody was iodinated with ^{123}I using the Iodogen method, with a final activity concentration of 20-60 mCi/mg IgG (Andres, 1988). As with other granulocyte labels, ^{123}I-AK-47 does not distinguish between abscesses and other types of inflammatory foci (Seybold, 1988). Hasler et al (Hasler, 1988) reported that 8-17% of the injected dose was associated with circulating granulocytes and the clearance of the antibody from the circulation fitted a biphasic model with effective half-lives of the components of 0.73 and 9.3 hr respectively. In five patients administered with 3.4-5.4 mCi of ^{123}I-AK-47 ($\sim 120\ \mu g$ antibody), clear images of the lesions were obtained at 30 min to 24 hr following injection. No HAMA was detectable in patients with small doses ($< 120 \mu g$) of the antibody. This antibody was also recently labeled with ^{99m}Tc using a new one-step method in which a free terminal amino group was utilized (Locher, 1991). When compared with ^{123}I-AK-47 in same patients, the distributions and scan qualities were observed to be similar although diagnostically relevant differences were noted in some cases of chronic osteomyelitis. The accuracy, sensitivity, and specificity of both methods averaged greater than 90%. These investigators concluded that ^{99m}Tc-AK-47 is more advantageous for routine use although ^{123}I-AK-47 is preferable in some cases of chronic infections (Locher, 1991).

A similar antibody, reported first by Bosslet et al (Bosslet, 1985) was later developed and produced as MAb BW-250/183 by Behringwerke AG, Germany (Table 1). It recognizes the same NCA-95 antigen on granulocytes and its in-vivo properties are very similar to MAb AK-47. Joseph et al (Joseph, 1988) were the first to label MAb BW 250/183 with ^{99m}Tc using the kit method of Schwarz and Steinsträsser (Schwarz, 1987; Steinsträsser, 1989). In a first step, free sulfhydryl groups are generated by reducing some of the disulfide bonds in the antibody using a thiol reagent (2-mercaptoethanol or others). Following column purification, 2mg of the reduced antibody is lyophilized in the presence of a pH 7.2 phosphate buffer. The second lyophilized reagent consists of stannous chloride and a phosphonate compound (usually pyrophosphate, methylene diphosphonate, or propanetetraphosphonic acid). The tin reagent is reconstituted with saline and an aliquot containing $\sim 10\ \mu g$ tin is added to the antibody vial, followed by the addition of ^{99m}Tc from the generator. Labeling yields are >95% and the labeled antibody can be injected without

further purification.

Table 1. Monoclonal antibodies for in-vivo labeling of human granulocytes

Antibody	Antigen	Radiolabel(s) used	Kd,M/L (Antigens/cell)	References(s)
CEA-47 (AK-47)	NCA-95	^{123}I ^{99m}Tc	6.8×10^{-9} (7.1×10^{4})	Buchegger,1984 Andres,1988
BW-250/183	NCA-95	^{99m}Tc	2×10^{-9} (7.1×10^{4})	Bosslet,1985 Becker,1989
MCA-480	Lacto-N-fuco-pentoase	^{99m}Tc, ^{111}In	1.6×10^{-11} (5.1×10^{5})	Thakur,1991
NCA-102	NCA-95	^{111}In	9.1×10^{-10}(IgG) 5.3×10^{-9}(Fab'$_2$) (1.2×10^{5})	Collet,1991

Technetium-99m-labeled BW 250/183 has been evaluated by a number of investigators. In one early study (Becker, 1989), 15 patients with suspected infections were studied. There was no change in the peripheral leukocyte count following the antibody injection. The recovery of ^{99m}Tc-MAb labeled granulocytes peaked at around 10%. There was a rapid binding of BW 250/183 with granulocytes in the bone marrow and spleen. The kinetics (with a typical lung and cardiac transit) were comparable with those of ^{111}In-oxine or ^{99m}Tc-HMPAO labeled granulocytes although the early curves (first 5 min) were different due to the necessity of slow antibody injections. The recovery rates are significantly lower than those of ^{111}In-oxine labeled granulocytes and this resulted in low lesion to background ratios with the use of the antibody. The general in-vivo behavior for both cases under

normal and activated conditions, however, was quite comparable. The delayed localization of infections with the antibody was attributed to a slow antigen-antibody reaction. Because of the amounts (~200 μg) of the antibody used, all granulocytes, circulating as well as those in the bone marrow, were labeled. It was suggested that abscess targeting resulted from a chemotactic attraction of the MAb-labeled cells rather than from MAb targeting of granulocytes within the abscess (Becker, 1990). In a recent study in 56 patients (Becker, 1991), the percent sensitivity, specificity and accuracy of the method, respectively, were 57, 89 and 71 at 4 hr and 86, 89, and 88 at 20 hr after injection. The recommended time for best images was 20 hr following administration. In a recent report (Berberich, 1991), 19 patients with inflammatory lesions were studied with the simultaneous injection of both ^{99m}Tc labeled 250/183 and ^{111}In-oxine labeled granulocytes. Two energy channels were used for simultaneous detection of ^{99m}Tc and ^{111}In. Clearance of radioactivity from blood as well as from whole body was much faster with ^{99m}Tc-MAb than with ^{111}In-oxine-granulocytes (31 and 11% remaining at 4 and 20 hr respectively in blood, vs 46 and 31% for ^{111}In). Cell bound ^{99m}Tc-MAb ranged between 18-25% at 0.5 to 20 hr after administration. Localization in bone marrow was higher but lower in liver/spleen compared to ^{111}In-oxine-granulocytes. Nearly all abscesses were localized within 4-6 hr post injection of the antibody. the statistical quality of ^{99m}Tc images, as expected, was superior. However, since a relatively larger number of cells get labeled with the antibody in vivo, especially in the bone marrow, results are somewhat impaired. Nonetheless, ^{99m}Tc-MAb 250/183 was found to be a very promising overall agent for imaging acute focal inflammatory lesions.

A yet another antibody (NCA 102) directed against the NCA 95 protein of granulocyte cell membrane was developed and investigated recently (Collet, 1991). F(ab')$_2$ fragments of this IgG1 antibody were produced and labeled with ^{111}In-DTPA. Upon incubating 100 μg F(ab')$_2$ with 30 ml blood (1 hr, 37°C), 30-35% of the radioactivity was bound to PMN leukocytes. Following the injection of 250 μg fragment labeled with 0.5 mCi ^{111}In, all infectious foci were imaged in five patients, and the lesion uptake corresponded well with ^{99m}Tc-HMPAO labeled leukocyte studies done 48 hr later.

A panel of ten monoclonal antibodies for human neutrophils was evaluated by Thakur et al (Thakur, 1988; 1990) in order to identify systems suitable for imaging inflammatory foci. Out of these, MCA-480, an IgM antibody reacting with the lacto-N-fucopentoase antigen, was found to be the most attractive for further development (Thakur, 1990, 1991) (Table 1). This antibody was labeled with ^{99m}Tc using the reduced antibody method (Thakur, 1990a) and with ^{99m}Tc and ^{111}In using the cyclic DTPA dianhydride method

(Hnatowich, 1983). Greater than 70% of the labeled antibody was found to bind to fresh human neutrophils in a saturable fashion. This antibody does not bind to granulocytes from the commonly used animal species and therefore its evaluation had to proceed directly in humans. In recent preliminary clinical studies (Thakur, 1991), the overall distribution of ^{99m}Tc-MCA-480 was found to be similar for both radiolabeling methods. Average percent distribution of radioactivity in blood 3 hr following injection (4 patients) was as follows: 36 ± 14 (PMN); 2.6 ± 1.3 (platelets); 9.4 ± 1.7 (lymphocytes); 1.5 ± 0.7 (RBC); and 51.6 ± 10.8 (plasma) (Thakur, 1991). Intestinal or thyroid uptake was absent in the 3-4 hr images. The radioactivity in the liver and spleen was, however, persistent as is also found to be the case with ^{111}In-oxine-WBC. Positive localization of administered ^{99m}Tc-MCA-480 was observed in patients with osteomyelitis and appendicitis. The exact mechanisms have not yet been elucidated (Thakur, 1991). The preliminary results look sufficiently promising to warrant further evaluation.

Lymphocytes

Very little work has been reported on the development of anti-lymphocyte monoclonal antibodies. There is, however, some interest in radiolabeled lymphocytes for the study of transplant rejection as well as for determining cellular kinetics and migration. Indium-111-oxine labeling imparts significant damage to the radiation sensitive lymphocytes since this agent is taken up into the cell and binds to intracellular components. Monoclonal antibodies that bind to lymphocyte surface antigens may offer an improvement in this regard. Preliminary results on labeling lymphocytes using monoclonal antibodies directed against cell surface antigens CD-2 and CD-4 have been reported recently. Immunoscintigraphic detection of transplant rejection (Baum, 1990), and the imaging of rheumatoid arthritis (Becker, 1990a) were investigated.

Conclusion

Blood cell labeling using monoclonal antibodies directed against specific cellular antigens is an area that has undergone exciting progress during the last five years. Even though the results thus far are preliminary, the technique does offer substantial future promise for the in-vivo labeling of various cells including leukocytes and platelets. In-vivo labeling would be a major advantage since it will eliminate the undesirable step of cell

separation that is required in existing methods. In-vivo labeled cells will be expected to better maintain viability and thus produce good localization. Also, a number of good imaging isotopes such as ^{99m}Tc, ^{123}I, and others can be used as labels for monoclonal antibodies (Srivastava, 1991). The whole body and organ doses are expected to be much less compared to In-oxine labeled cells. In principle, it would also be possible to differentiate between different types of lesions and infections. Despite these advantages and future promise, however, a number of problems and concerns remain yet to be addressed. Development of chimeric and human antibodies may eliminate or minimize the HAMA problem that is frequently experienced with the use of murine antibodies. Normal tissue cross reactivity could be overcome with the identification and development in the future of antibodies with higher specificity and avidity for particular cell surface antigens. Future prospects for such improvements indeed look very promising at this point.

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