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**Antibodies – unmaturred and maturated defenders against cancer**

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32 Antibodies (Abs) are glycoprotein molecules which represent an essential component of the  
33 adaptative immune response. They are secreted in body fluids and act as a critical part of the  
34 immune defense. Although recognition of self-antigens by Abs is normally counter-selected  
35 during the ontogeny of B cells, autoreactive Abs can be generated in result of pathological  
36 immune response as observed in autoimmune diseases. Autoantibodies can also be produced  
37 in cancer patients where they may have beneficial roles.<sup>1</sup> Indeed, the presence of intratumoral  
38 antibody-secreting cells (ASCs) and B-cell-rich tertiary lymphoid structures (TLSs) have been  
39 observed in many cancer types and generally correlate with a favorable clinical prognosis.<sup>2-6</sup>  
40 The existence of specific anti-tumor antibody responses suggests that tumor cells express  
41 molecules that are recognized as non-self antigens by immune system or that the tolerance to  
42 self-antigens expressed on cancer cells is lost.<sup>1,4</sup> The study of the origin of tumor-reactive Abs,  
43 their specificity and functions are of paramount importance to figure out the development of  
44 adaptive anti-tumor immune response and to find novel therapeutic avenues. A recent  
45 publication in *Cell* by Mazar et al.<sup>7</sup> has provided an important advance in our understanding  
46 about antibody responses in cancer. Particularly, this work paves the way for distinction  
47 between antibody-reactive tumors versus antibody non-reactive tumors, that is reminiscent  
48 with the concept of non-infiltrated “cold” tumor microenvironment (TME) in opposition with  
49 highly-infiltrated “hot” TME.<sup>8</sup> Moreover, an important finding of this study is the  
50 demonstration that tumor-directed autoreactivity may be both pre-existing or induced by  
51 somatic hypermutations, a mechanism related to the chronicity of cancer disease.

52

53 In their study, Mazar et al.<sup>7</sup> examined tumor samples from untreated high grade serious ovarian  
54 cancer (HGSOC) patients. The samples were stained for IgG Abs and by using a machine  
55 learning approach, the localization of IgG was analyzed by histology. Data showed that many  
56 of HGSOC primary tumors had deposit of endogenous IgG molecules at levels which are much

57 higher than the level of background IgG deposits detected in healthy ovarian tissue (64 vs 10%,  
58 respectively). The authors further confirmed this observation on live epithelial and metastatic  
59 cells using flow cytometry. Furthermore, after purification of polyclonal IgGs from tumor  
60 ascites, the binding of Abs to cancer cells was studied and shown that 72% of ascites contained  
61 IgG specific for tumor cells. Importantly, using immunohistochemistry and flow cytometry  
62 analysis, the authors revealed that tumor samples present tertiary lymphoid structures (TLS)-  
63 like clusters with more than half of the intratumoral ASCs producing IgG1 Abs. These results  
64 imply that endogenous tumor-reactive Abs, probably produced by intratumoral ASCs, can bind  
65 the surface of ovarian cancer cells. The binding of endogenous Ab to tumor cells might be a  
66 frequent feature of anti-tumoral immune responses because it was also found in several other  
67 types of cancers tested in the present study and other studies, particularly in renal and urothelial  
68 carcinoma.<sup>6,7</sup> Importantly, Mazor et al. demonstrated that the presence of IgG producing ASC  
69 and deposits of IgG on the surface of tumor cells was associated with a significantly better  
70 prognosis for patients with HGSOE, these findings being in line with the positive impact of the  
71 presence of B-cell containing TLS observed in several cancers.<sup>4-6,9,10</sup>

72 An essential aspect of the work of Mazor et al. is the investigation of the origin of anti-tumor  
73 specificity of autoreactive B cells infiltrating the tumor. After a single cell sorting from fresh  
74 tumor samples, the authors sequenced the genes encoding V<sub>H</sub> and V<sub>L</sub> domains of infiltrating  
75 IgG1<sup>+</sup> ASC. They found that sequences encoding the variable domains in these cells present a  
76 high level of somatic hyper mutations (SHM) that is in the same range as the one documented  
77 for human memory B cells. Moreover, the reconstruction of cell lineages of the intratumoral  
78 ASCs showed high degree of clonal relationship, suggesting that a considerable portion of  
79 intratumoral B cells originate from a few common ancestors.

80 In a next stage of the study the authors cloned from intratumoral ASC and expressed a  
81 repertoire of recombinant IgG1 Abs. This repertoire contained representative Abs from

82 different clonal families and it was used for mechanistic and functional studies. Importantly, a  
83 significant fraction of the recombinant Abs (15/27) demonstrated binding reactivity towards  
84 primary ovarian cancer cell cultures. To assess the impact of SHM on anti-tumor Ab  
85 specificity, the authors reverted the sequences encoding V<sub>H</sub> and V<sub>L</sub> domains into their germline  
86 versions and they observed, using immunofluorescence assays, that half of the tumor-reactive  
87 Abs lost their binding capacity to cancer cells after reversion to germline. This result suggests  
88 that anti-tumor specificity of Abs in patients with ovarian cancer is both natural (germline  
89 encoded) and acquired as a consequence of affinity maturation and selection of B cells. The  
90 generation of novel autoreactivities of Abs as a result of insertion of SHM into immunoglobulin  
91 genes was described before.<sup>11</sup> Autoreactive Abs detected in cancer patients traditionally come  
92 from self-reactive B cells that have escaped the tolerance mechanisms that occur during the B  
93 cell ontogeny.<sup>1,4</sup> Acquisition of SHM typically takes place in germinal centers that can be  
94 located in lymph nodes as well as in intratumoral tertiary lymphoid structures. The latter have  
95 been associated to generation of intratumoral ASCs producing Abs directed towards tumor-  
96 associated antigens in various cancers.<sup>4</sup> Thus, we can conclude that in addition to naturally  
97 autoreactive Abs that are specific to the tumor antigen, Abs that do not bind a self-target tumor  
98 antigen in their original germline version may be positively selected during B cell maturation  
99 for their newly acquired tumor specificity.

100 In addition to affinity matured Abs, unmatured Abs with germline configuration of their V  
101 genes have been demonstrated to play an important role in anti-tumor defense in animal  
102 models. Thus, several recent studies revealed that natural IgM Abs contribute for tumor  
103 elimination in mice.<sup>12-14</sup> These studies showed that the presence of neoantigens on cell surface  
104 results in a binding of natural IgM Abs, a process that triggers elimination of the modified cells.  
105 In contrast to Abs identified in the study of Mazor et al., the natural IgM Abs are frequently  
106 polyreactive. Hence they can have distinct mode of action in protection against cancer. It was

107 proposed that these natural auto-reactive Abs may increase the immunogenicity of tumor cells  
108 by allowing antigen-presenting cells to present cognate tumor antigens to specific T cells.<sup>14</sup> It  
109 remains to be clarified whether in humans the Abs with germline configuration and specificity  
110 for tumor antigens exert similar anti-tumoral effect and also whether they can trigger the loss  
111 of self-tolerance and generation of tumor-reactive autoantibodies following SHM process as  
112 observed in the study of Mazor et al.

113 Further, Mazor et al. used the repertoire of recombinant Abs to identify the target antigens on  
114 cancer cell. The authors identify the matrix metalloproteinase 14 (MMP14) as a major target  
115 for the patient-derived Abs. They observed a milder cross-reactivity to other  
116 metalloproteinases, but they did not detect reactivities to other human antigens. It is noteworthy  
117 that MMP14 is overexpressed by tumors and contributes along with other metalloproteinases  
118 for remodeling of extracellular matrix and tumor invasion.

119 Finally, Mazor et al. studied the Fc-mediated functions of recombinant Abs as well as of  
120 polyclonal IgG isolated from tumor ascites. It was found that polyclonal Abs and some of the  
121 recombinant Abs were efficient to induce antibody-dependant cellular cytotoxicity (ADCC) by  
122 NK cells and antibody-mediated cell phagocytosis (ADCP) by monocytes. Although these Abs  
123 bind efficiently to tumor cells, cytotoxic effector cells might be rare in HGSOE patient tumors  
124 and their recruitment in the tumor microenvironment can be difficult. Therefore, it remains  
125 unclear if the beneficial effect on patient survival of the presence of IgG in the tumor is  
126 mediated through activation of effector functions by anti-tumoral Abs or they exert effect  
127 through other mechanisms. In this respect, it will be interesting to be elucidated what are the  
128 functional consequences of Ab binding on the enzyme activity of metalloproteinase. If Abs  
129 inhibit the remodeling of extracellular matrix, this suggests that Mazor and colleagues  
130 identified a putative therapeutic target for cancer therapy with Abs. Moreover, it is important

131 to understand whether the metalloproteinases are typical target for humoral responses against  
132 other types of cancer or they are specific only for HGSOc.

133 In conclusion the study of Mazor and al. represents an important step in understanding antibody  
134 responses against cancer. This study clearly highlights that there is a specific selection and  
135 affinity maturation of high affinity autoreactive B cells targeting tumor antigens (**Figure 1**). In  
136 view of the fact that mAbs produced in tumor microenvironment are directed against self-non-  
137 mutated proteins rather than being restricted to tumor-specific antigens, this study highlights  
138 the close relationship between self-tolerance breakdown and anti-tumor immunity. *In situ* high  
139 expression of particular self-antigens (e.g., in ovarian and pancreatic cancers which are highly  
140 fibrotic, a protein involved in the remodeling of the extracellular matrix) combined with pro-  
141 inflammatory environment might promote tolerance breakdown. Interestingly, although Mazor  
142 et al. report in this study that self-reactive antibodies formed in cancer patients have the  
143 potential to bind healthy tissues in addition to tumor cells, no signs of autoimmunity have been  
144 detected. Moreover, large-scale retrospective study of patients with ovarian cancer over a  
145 follow-up period of up to 15 years did not reveal increased incidence of autoimmune diseases,  
146 raising questions about the relation between autoreactivity and autoimmune manifestations.  
147 The non-persistence over the long term of sera autoantibodies produced in cancer patients and  
148 the deleterious impact of certain therapies such as chemotherapy on the production of  
149 antibodies by B lymphocytes are among the hypotheses given by the authors to explain this  
150 absence of autoimmunity occurrence. This issue is different in patients treated with anti-PD-1  
151 and/or anti-CTLA-4 mAbs, since these treatments, on the contrary, probably potentiate the  
152 reactivation of autoreactive (probably also anti-tumor) B-cell clones, promoting the  
153 development of various autoimmune side effects in treated patients.<sup>15</sup>

154 The study opens numerous questions. By addressing these questions, important fundamental  
155 insights and novel therapeutic approaches can be gained.

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200

### 201 **Figure legend.**

#### 202 **Role of unmaturred and matured antibodies in anti-cancer immune defense**

203 Hypothetical overview of the development of a humoral immune response directed against the  
204 tumor. Natural germline-encoded tumor-binding Abs can recognize overexpressed antigen or  
205 neoantigen on the tumor cell surface at early stage of tumorigenesis (1). These Abs increase  
206 the immunogenicity of tumor cells (2), which leads to tumor cell destruction and/or to the  
207 recruitment of immune cells such as antigen-presenting cells (3,4). Then, activation of tumor-  
208 specific T cells in intratumoral TLS allows B cells that do not recognize these antigens to enter  
209 the maturation process and acquire specificity to tumor antigen through SHM (5). Finally,  
210 matured B cells differentiate into ASCs that produce another type of tumor-reactive Abs (6)  
211 and participate in the humoral anti-tumor immune response through antibody-dependent  
212 mechanisms (ADCC, ADCP) (7). Figure was prepared using BioRender  
213 (<https://biorender.com/>).

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