Receptors for Interleukin (IL)-4 Do Not Associate with the Common γ Chain, and IL-4 Induces the Phosphorylation of JAK2 Tyrosine Kinase in Human Colon Carcinoma Cells*

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We have previously reported on the expression of interleukin-4 receptors (IL-4R) on many human epithelial cancer cells; however, the binding characteristics, structure, function, and signal transduction through the IL-4R in cancer cells is not known. IL-4 binding characteristics were determined in human colon carcinoma cell lines by a 125I-IL-4 binding assay, which demonstrated that the HT-29 and WiDr colon cancer cell lines expressed high affinity IL-4R (Kd = 200 pm). Cross-linking experiments revealed a major band of 140 kDa and a broad band at 70 kDa. While the common γ chain of IL-2R is associated with IL-4R in immune cells and is similar in size to the 70-kDa protein, this chain was not expressed in these colon cancer cells. Interestingly, IL-13, which has many functions similar to IL-4, inhibited 125I-IL-4 binding to both the 140- and 70-kDa molecules. Next, we investigated the mechanism of IL-4-induced signal transduction in colon cancer cells. After stimulation with IL-4, a 170-kDa band was primarily phosphorylated within 1 min of exposure and was identified as insulin receptor substrate-1. In addition, by immunoprecipitation assay, three other phosphorylated bands were identified as JAK1, JAK2, and Tyk2 tyrosine kinases. The phosphorylation of JAK1 and JAK2 was induced by IL-4 stimulation; however, Tyk2 was constitutively phosphorylated, and IL-4 treatment further augmented this phosphorylation. The kinetics and in vitro kinase assays demonstrated that JAK1, JAK2, and Tyk2 were phosphorylated within minutes and that JAK1 and JAK2 were activated after IL-4 exposure. Contrary to observations in immune cells, JAK3 mRNA was not detected in colon cancer cells nor did IL-4 treatment cause phosphorylation of JAK3. These data indicate that in colon carcinoma cells JAK1, JAK2, Tyk2, and insulin receptor substrate-1 are phosphorylated after IL-4 stimulation. In addition, as is the case in lymphoid cells, IL-4 activated and phosphorylated signal transducers and activators of transcription (IL-4-STAT or STAT-6) protein in both colon cancer cell lines. These results indicate that the IL-4R complex is composed of different subunits in different tissues and shares a component with the IL-13R complex. In addition, we demonstrate for the first time that like its family members (e.g. IL-3 and GM-CSF), IL-4 can phosphorylate and activate JAK2 kinase.

IL-4 is a growth and differentiation factor of human B- and T-lymphocytes (1-3). In contrast to its growth stimulatory effects on lymphocytes, IL-4 has a growth inhibitory effect on many human carcinoma cells. We (4, 5) and others (6-8) have reported that IL-4 can inhibit the growth of human melanoma, colon, breast, and renal cell carcinomas in addition to cells of hematologic malignancies (9-11). It has been shown that IL-4 receptors are expressed on a variety of cell types (12-14) and that IL-4 functions by signaling through its receptors (15). However, the mechanism for the opposing biological activities elicited by IL-4 is not clear.

While the structure of the IL-4R has been studied extensively, it has not been fully characterized. Cross-linking studies using 125I-IL-4 have revealed that, on human cells, radiolabeled IL-4 cross-linked to one major protein of 140 kDa, and in some cases, one or two additional bands were cross-linked (70-80 and 65-70 kDa) (16-19). In COS-7 cells transfected with the human IL-4R cDNA, radiolabeled IL-4 bound to a 140-kDa protein (15, 20); however, this binding was not sufficient to cause IL-4 signaling (20). Cotransfection of the IL-2R γ chain (a 64-kDa protein, termed γc) into these COS-7 cells (20) caused IL-4-induced phosphorylation of insulin receptor substrate-1 (IRS-1). These data suggest that γc is associated with the 140-kDa protein of IL-4R, and this association is necessary for signaling in these cells. Subsequently, the γc chain has been shown to be utilized in other receptor systems, such as those for IL-7, IL-9, and IL-15 (20-24). The identity of the 70-80-kDa IL-4 cross-linked species is still not clear. Previously, it was thought to be a breakdown product of the 140-kDa protein (25), although recent studies have identified a low affinity 70-kDa IL-4 protein (26).

More recent studies have examined the mechanism of IL-4 signaling in different cell types. As a member of the hematopoietin family and cytokine receptor family (27), IL-4R has no consensus sequence motifs for tyrosine and/or serine/threonine kinases in its intracellular domain (15, 28). However, IL-4R has been reported to associate with tyrosine kinases and induce tyrosine phosphorylation of 110-, 140-, and 170-kDa proteins in murine cell lines (29, 30). The 140-kDa protein has been shown to be an IL-4 binding receptor protein (31, 32), and the 170-kDa protein was designated 4PS, which is similar to IRS-1 (32, 33). It was demonstrated that IRS-1 or 4PS expression is necessary

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The abbreviations used are: IL-4, interleukin-4; IL-4R, IL-4 receptors; IRS-1, insulin receptor substrate-1; PAGE, polyacrylamide gel electrophoresis; PVDF, polyvinylidene difluoride; RCC, renal cell carcinoma.
for efficient IL-4 and insulin-mediated mitogenic signaling in 3D cells (34, 51). In addition, it has been shown that the 140-kDa IL-4R protein associates with and activates, by phosphorylation, members of the Janus kinase family (JAK) (35). The JAK family consists of four members, JAK1, JAK2, JAK3, and Tyk2. Recently, it has been shown that IL-4 stimulated the proliferation of D10 T cells and that this proliferation was correlated with the phosphorylation of the JAK1 and IRS-1 (36) proteins upon ligand-receptor interaction. Association of the JAK3 kinase with IL-2R and IL-4R complexes has also been demonstrated (37–40). Furthermore, it has been suggested that as association between γc and JAK3 is essential for signaling through IL-2R system, the malfunction of γc-JAK3 pathway is believed to be tied to X-linked severe combined immune deficiency syndrome or XCID (23). However, the steps involved in the signaling pathways leading to growth inhibition of tumor cells triggered by IL-4 are not known.

In the current study, we examined the binding characteristics, structure, function, and signaling through the IL-4 complex on human colon carcinoma cells. Our data indicate that the IL-4R complex on colon carcinoma cells is composed of a predominant 140-kDa protein and a diffuse band suggesting a 70-kDa protein. By Northern analysis, cross-linking, and immunoprecipitation, it was demonstrated that while the common γc is not associated with the IL-4R system on colon cancer cells, these IL-4R receptors were functional because IL-4 caused phosphorylation of signaling proteins and inhibited the growth of these cells in tissue culture. To characterize the IL-4 signaling pathways in colon carcinoma cells, we examined the patterns of protein phosphorylation upon stimulation with IL-4. We report here that IL-4 induced tyrosine phosphorylation of JAK1, JAK2, Tyk2, and IRS-1 but not JAK3 proteins in colon cancer cells. We further demonstrate that the STAT-6 protein was phosphorylated and activated by IL-4 treatment.

**EXPERIMENTAL PROCEDURES**

Materials—Recombinant human IL-4 was kindly provided by Sche- ring Corp. (Kenilworth, N. J.). Polyclonal antibodies against JAK1, JAK2, Tyk2, IRS-1, and phosphotyrosine (Tyr-phospho; Zymed) were purchased from Upstate Biotechnology, and STAT-6 antibody was purchased from John O’Shea of the National Institutes of Health. Anti-mouse and rabbit IgG and horseradish peroxidase-conjugated antibodies were from Amersham.

Cells—Human colon cancer cell lines, WiDr and HT-29, and H9T cell lines were obtained from American Type Culture Collection. Cells were cultured in Eagle’s minimum essential medium with amino acids, 25 mM HEPES, and 10% fetal bovine serum.

Receptor Binding Assay—Recombinant human IL-4 was labeled with 125I (Amersham Corp.) by the IODO-GEN iodination reagent (Pierce). 125I (Amersham Corp.) by the IODO-GEN iodination reagent (Pierce) was determined by the "Ligand" program (42).

**RESULTS**

**IL-4 Binding Characteristics and the Effect of IL-4 on Colon Tumor Cell Growth**—The expression and binding affinity of IL-4R on colon carcinoma cell lines was determined by 125I-IL-4-receptor binding assay (Fig. 1, A and B). HT-29 and WiDr colon tumor cell lines bound IL-4 in a concentration-dependent manner. Scatchard plot analysis of the binding data indicated that a single class of high affinity IL-4R was expressed but...
on the proliferation of these cells by [3H]thymidine incorporation, cancer cells were functional, we investigated the effect of IL-4 on WiDr cells. Variations with cell line (6034 vs. 101) were observed when cross-linking was performed in the presence of 200-fold molar excess of IL-4, indicating that the observed bands are involved in specific IL-4 binding sites on WiDr cells compared to HT-29 cells, explaining the lower responsiveness to IL-4.

To determine whether the IL-4 receptors expressed on colon cancer cell lines are functional, we investigated the effect of IL-4 on the proliferation of these cells by [%H]thymidine incorporation assay. IL-4 inhibited tumor cell growth in both cell lines in a dose-dependent manner. Maximal growth inhibition (50%) occurred at >10 ng/ml (data not shown); however, the IL-4-induced growth inhibitory effects were less pronounced in the WiDr colon cancer cell line. It is possible that the lower number of IL-4 binding sites on WiDr cells compared to HT-29 cells explains the lower responsiveness to IL-4.

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Structure and Signal Transduction through IL-4 Receptor

A

B

FIG. 1. Expression of high affinity IL-4R on HT-29 and WiDr cells. Displacement curve (A) and Scatchard analyses (B) were generated from the binding data using the LIGAND program.

We next investigated whether IL-4 induced phosphorylation of IL-4R p140 protein. HT-29 cells were either left untreated or treated with IL-4 for 5 min (Fig. 3C, lane 1), cell lysate was immunoprecipitated with anti-IL4R p140 specific antibody, and immunoblotting was performed with 4G10. As shown, IL-4 induced phosphorylation of the IL-4R p140 protein.

The identity of the kinase involved in the phosphorylation of both proteins, IRS-1 and IL-4R 140 kDa, is not shown. Yin et al. (36) reported that in T cells JAK1 forms complexes with IL-4R p140 and IRS-1/4PS proteins, indicating that JAK1 may phosphorylate both IRS-1/4PS and IL-4R p140 proteins.

Phosphorylation of JAK1, JAK2, and Tyk2—To determine whether the JAK family kinases were involved in IL-4-induced signal transduction, cell lysates from both untreated and IL-4-treated colon cancer cell lines were immunoprecipitated with antibodies to JAK1, JAK2, JAK3, and Tyk2, electrophoresed, blotted on PVDF membrane, and immunoblotted with anti-phosphotyrosine antibody (Fig. 4A). We found that IL-4 induced phosphorylation of JAK1 and JAK2 kinases. Tyk2 kinase was constitutively phosphorylated at low levels in both cell lines, and IL-4 treatment further enhanced the phosphorylation of Tyk2 tyrosine kinase. However, these cells did not express JAK3 (by Northern analysis), and no phosphorylation of the JAK3 protein was observed (data not shown).

The kinetic studies were next undertaken, which indicated that the tyrosine phosphorylation of JAK1 and JAK2 occurred within 1 min following incubation with IL-4. This IL-4-induced phosphorylation reached a maximum at 5 min for JAK1 (Fig. 4B) and 5–10 min for JAK2 (Fig. 4C). The constitutive phosphorylation of Tyk2 was also increased within 1 min of IL-4 treatment, and this increase reached a maximum at 5 min after the addition of IL-4.
Samples were electrophoresed, and blots were probed with the immunoprecipitated anti-STAT-6 antibody (Fig. 6). IL-4 stimulated control and IL-4 treated (5 min) cell lysates showed phosphorylation of STAT-6 (IL4-STAT) in HT-29 cells after kinase assay (Fig. 4). JAK2 antibody, this band corresponded to JAK3 (Fig. 5, lane 1). Molecular weight markers are shown on the left. Upper arrow on the left of A corresponds to 140 kDa, and the lower arrow corresponds to 70-kDa proteins. B, immunoprecipitation of 125I-IL-4R complex with anti-γc antibody. Note the lower arrow in this figure corresponds to the 63-kDa protein. C, Northern blot analysis for γc. Total RNA (20 μg) from cell lines was electrophoresed in formaldehyde/agarose gels, transferred to membranes, and probed with cDNA of γc. Equivalent RNA loading was ascertained when this blot was rehybridized with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) cDNA. The positions of 28S and 18S RNAs are shown on left.

Fig. 2. IL-4 receptor structure analysis on colon cancer cell lines. A, HT-29 and WiDr cells (5 × 10^6) were labeled with 125I-IL-4 in the absence (lanes 1 and 4) or presence of excess unlabeled IL-4 (lanes 2 and 5) or IL-13 (lanes 3 and 6). Molecular weight markers are shown on the left. Upper arrow on the left of A corresponds to 140 kDa, and the lower arrow corresponds to 70-kDa proteins. B, immunoprecipitation of 125I-IL-4R complex with anti-γc antibody. Note the lower arrow in this figure corresponds to the 63-kDa protein. C, Northern blot analysis for γc. Total RNA (20 μg) from cell lines was electrophoresed in formaldehyde/agarose gels, transferred to membranes, and probed with cDNA of γc. Equivalent RNA loading was ascertained when this blot was rehybridized with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) cDNA. The positions of 28S and 18S RNAs are shown on left.

IL-4 Causes Activation of JAK1 and JAK2 Kinases—To investigate whether IL-4 stimulation of HT-29 cells resulted in increased phosphotransferase activity of JAK1, JAK2, and Tyk2 kinases, we immunoprecipitated JAK1, JAK2, and Tyk2 from control or IL-4-stimulated HT-29 cells. The enzymatic activity was determined by in vitro kinase assay. Our data revealed that JAK1 and JAK2 were autophosphorylated (Fig. 4). As expected, IL-4-stimulated cells caused phosphorylation of JAK1 and JAK2 proteins, and this phosphorylation was increased when immunoprecipitates were incubated in the presence of ATP. A certain basal level of kinase activity was seen when Tyk2 was incubated with ATP, and stimulation with IL-4 did not appreciably increase this activity. No basal activity of JAK1 or JAK2 was observed. These results suggest that both JAK1 and JAK2 kinases are activated in HT-29 colon cancer cells following IL-4 stimulation.

JAK2 Was Not Phosphorylated in Human T Cells—Previous studies have reported that IL-4 did not stimulate phosphorylation of JAK2 kinase in human TF-1, murine D10, CTLL T lymphocytes, and FD5 cell lines (36, 39, 40, 50). We examined whether JAK2 was phosphorylated in response to IL-4 in human T cells. Cell lysates from control and IL-4 stimulated human T cell line (H9) were immunoprecipitated with anti-JAK2 antibody and analyzed for phosphorylation. IL-4-stimulated cells showed phosphorylation of one major protein of ~116 kDa (Fig. 5, lane 1). When this blot was stripped and blotted with JAK2, the size of the phosphorylated band appeared to be smaller than the expected JAK2 band (Fig. 5, lanes 3 and 4). Upon reblotting with JAK3, without stripping JAK2 antibody, this band corresponded to JAK3 (lanes 5 and 6). These data suggest that IL-4 did not phosphorylate JAK2 kinase in human T cell line while JAK3 was phosphorylated in T cells as shown previously (36, 39, 40).

Phosphorylation of STAT-6 Protein—To examine whether JAK1, JAK2, and Tyk2 kinase activation resulted in tyrosine phosphorylation of STAT-6 (IL4-STAT) in HT-29 cells after IL-4 stimulation, control and IL-4 treated (5 min) cell lysates were immunoprecipitated with anti-STAT-6 antibody (Fig. 6). Samples were electrophoresed, and blots were probed with anti-phosphotyrosine antibody. The results indicate that as in lymphoid cells (43–45), IL-4 induced phosphorylation of the STAT-6 protein in HT-29 and WiDr colon cancer cells. Even though cell lysates from an equal number of cells from control and IL-4-treated cells were analyzed for STAT-6 phosphorylation, immunoblots always generated a pattern indicating unequal loading of the gel. IL-4-stimulated cells always showed higher concentration of STAT-6 protein. We believe that since STAT-6 protein normally resides in monomeric form in the cytosol and undergoes dimerization after stimulation, it is possible that antibody to STAT-6 protein is more reactive to dimer than to monomer and that is why we see unequal amounts of protein in control and IL-4-stimulated cells.

DISCUSSION

In this study, we demonstrate that human colon carcinoma cell lines express high affinity IL-4R and that these receptors are functional since IL-4 inhibited their growth in tissue culture. The IL-4R on these colon cancer cells seemed to be composed of two major proteins with a molecular mass of 140 and 70 kDa. The 140-kDa IL-4R protein has been well characterized (28); however, the exact identity of the 70-kDa protein is not clear. It was previously thought that the 70-kDa protein was a proteolytically degraded product of the larger 140-kDa protein (19). However, other studies (20, 21) have demonstrated that IL-2R common γ chain (64 kDa), which is similar in size to the 70-kDa protein, is a component of the IL-4R complex in immune cells. Thus, it is possible that the common γ chain is also a component of the IL-4R complex in colon cancer cells. To determine the identity of the 70-kDa IL-4R subunit, two types of experiments were performed. First, cell lysates were immunoprecipitated with antibody to γc (23) and analyzed on SDS-PAGE. These data demonstrated that although monoclonal antibody to γc immunoprecipitated a 64- and 140-kDa protein in phytohemagglutinin-activated T cells, no bands were immunoprecipitated in the colon cancer cell lines examined (Fig. 2, A and B). Second, by Northern analysis, mRNA for γc was not detected in either colon cancer cell line. Thus, unlike human B and T cells, the IL-4R complex on colon cancer cells does not utilize the common γc chain for the func-
The appearance of both 125I-IL-4 cross-linked p70 and p140 bands that has many activities similar to IL-4 (46, 47), inhibited the is of interest to note that IL-13, a recently discovered cytokine

...tion of IL-4.

...tion of IRS-1 on the human TF-1 cell line, which expressed

...kinase.

...ket of IL-4-induced inhibition of tumor cell growth in vitro, we investigated the mechanism of signal transduction by IL-4 in colon cancer cells. We have demonstrated that IL-4-induced signaling events in colon carcinoma cell lines are different from those reported on immune cells (36, 39, 40, 50). In both colon carcinoma cell lines, AK1, JAK2, Tyk2, and 4PS/IRS-1 proteins were tyrosine phosphorylated in response to IL-4. These data partially agree with recent reports in which IL-4 was found to phosphorylate AK1 and 4PS/IRS-1 in T cells, NK cells, and myeloid cells (36, 37, 39, 40). Similarly, in a recent study Tyk2 was also shown to be phosphorylated after IL-4 stimulation of human erythroleukemia (TF-1) and murine plasmacytoma cell lines (B9) (40). However, in contrast to previous reports utilizing immune cells (39, 40, 50), JAK3 kinase was not phosphorylated in response to IL-4 in colon cancer cells. These data corroborated with Northern analysis and immunoprecipitation data and showed that both colon cancer cell lines studied did not express JAK3 mRNA (data not shown). In addition, the phosphorylation of JAK2 protein by IL-4 was not seen in the reports using immune cells, e.g. CTLL T lymphocytes, D10 T lymphocytes, TF-1, and FD-5 cell lines (36, 39, 40, 50), whereas we demonstrate JAK2 utilization by IL-4 in colon cancer lines. Our data provide the first report that shows that, like the other members of the IL-4 family of lymphokines (e.g. GM-CSF and IL-3) (56, 57), IL-4 can induce phosphorylation and activation of JAK2 tyrosine kinase.

It has been previously reported that the common γc chain is required for tyrosine phosphorylation of IRS-1 in response to IL-4 in immune cells (20). It has also been reported that expression of the common γc chain, in addition to IL-4R p140, is required for the proliferation of mouse F7 cells in response to IL-4 (60). However, colon carcinoma cells did not express γc chain, yet the phosphorylation of IRS-1/4PS was observed. Our data suggest that another protein, the 70-kDa protein identified here, may function instead of γc in HT-29 cells to help phosphorylate IRS-1 in response to IL-4.

In previous studies, IRS-1 was shown to be phosphorylated in response to IL-4 only in murine cells (32, 33, 36), and no phosphorylation was observed in human cells transfected only with human IL-4R 140-kDa protein (20, 52). However, a recent study reported that IL-4 caused phosphorylation of IRS-1 on the human TF-1 cell line, which expressed γc (53). Our results agree with this report and provide direct evidence that IL-4 can also cause phosphorylation of IRS-1/4PS in human colon cancer cells without the presence of γc. The type of kinase that utilizes IRS-1/4PS as a substrate is still unclear. Since AK1 and IRS-1/4PS have been shown to associate with the IL-4R p140 protein in murine T cells (36), it is possible that AK1 phosphorylates IRS-1/4PS. Furthermore, since Tyk2 and JAK2 were also phosphorylated by IL-4 in colon cancer cells, it is possible that these kinases also utilize IRS-1/4PS as a substrate.
Following the Janus kinase family activation, tyrosine phosphorylation and activation of the STAT family of transcription factors may follow (54). Recently, growth factors and cytokines including IL-4 have been shown to activate specific STAT proteins (43–45). For example, IL-4 has been reported to activate IL-4 STAT/STAT-6 in immune cells (44, 45). Similarly, in the present study, we found that IL-4 was able to activate STAT-6 in both colon carcinoma cell lines.

It is clear that IL-4 has contrasting effects on the growth of different cell types. In antigen-specific T helper lymphocytes (D10) and other human immune cells (36, 55), IL-4 has potent

**FIG. 4.** Tyrosine phosphorylation of JAK1, JAK2, and Tyk2 kinases and time course. HT-29 and WiDr cells were stimulated with IL-4 for 5 min or not stimulated (A) or HT-29 cells were stimulated for various periods of time (B–D). Cell lysates (2 × 10^7 cells/sample) were immunoprecipitated with indicated antibodies as described in Fig. 3. Immunoprecipitates were separated by 8% SDS-PAGE, transferred to PVDF membranes, and immunoblotted with 4G10 antibody. Then, membranes were stripped and reimmunoblotted with anti-JAK1, JAK2, and Tyk2 and visualized by ECL. Control and IL-4-pretreated HT-29 cells were subjected to anti-JAK1, Tyk2, and JAK2 immunoprecipitation for in vitro kinase assay (E). Cell lysates from 20 × 10^6 cells/lane were utilized. Blots were stripped and reblotted with anti-JAK1, Tyk2, and JAK2 antibodies. As seen, band intensities were darker in IL-4+ATP-treated lanes compared to IL-4 and no ATP lanes for JAK1 and JAK2 tyrosine kinases; however, no change in band intensity was observed with Tyk2 kinase.

**FIG. 5.** IL-4 does not phosphorylate JAK2 in T cells. H9 cells were stimulated with IL-4 for 5 min, and cell lysates were immunoprecipitated with anti-JAK2, electrophoresed on 8% SDS-PAGE, and immunoblotted with antiphosphotyrosine antibody. The blot was stripped and reblotted with anti-JAK2 and JAK3 antibodies. The positions of the molecular weight markers are shown on the left, and proteins of interest are shown on right.

**FIG. 6.** Phosphorylation of IL-4 STAT. HT-29 and WiDr cells were treated with IL-4 for 5 min, and then cell lysates from an equal number of control and IL-4 stimulated cells were immunoprecipitated with anti-STAT-6 antibody. Samples were electrophoresed, and blot was hybridized with anti-phosphotyrosine antibody. Molecular weight markers are shown on the left, and proteins of interest are shown on right. In many experiments, even though we used equal number of cells in control and IL-4 treated cells, still unequal amounts of STAT-6 were detected by blotting with anti-STAT-6 antibody. However, in all experiments, no phosphorylation of STAT-6 protein was observed in control cells, but IL-4 treated cells showed significant phosphorylation.
three subunits. In some cells, IL-4R may share γc, while in other cells it may share a chain with the IL-13R complex; yet still in other cell types all three chains may be present. The latter model of IL-4R may resemble that of the IL-2R system, which is also composed of a trimeric complex.

Finally, even with the contrasting effects on immune and tumor cells, IL-4 induces rapid phosphorylation of JAK1, Tyk2, 4PS/RS-1, and STAT-6 proteins in both types of cells. However, JAK2 was neither present nor phosphorylated in these tumor cells. Furthermore, we report for the first time that JAK2 is phosphorylated and activated in response to IL-4. Thus, differences in the subunit structure of the IL-4 receptor and IL-4 signaling pathways exist between tumor cells and immune cells. Additional studies are necessary to determine whether one or both of these differences may be responsible for contrasting functional effects of IL-4.

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CONCLUSION

Our data demonstrate that the IL-4R complex on human colon carcinoma cells is different from that expressed on immune cells (see schematic model in Fig. 7). Unlike immune cells, IL-4R on colon cancer cells do not utilize the common γc otherwise shared between the receptors for IL-2, IL-4, IL-7, IL-9, and IL-15. Based on our data and published information, we propose that the IL-4R system may be composed of two to
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