Are Peroxisome Proliferator-Activated Receptors Involved in Skeletal Muscle Wasting during Experimental Cancer Cachexia? Role of \(\beta_2\)-Adrenergic Agonists

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Abstract

Implantation of the Yoshida AH-130 ascites hepatoma to rats resulted in a decrease in muscle weight 7 days after the inoculation of the tumor. These changes were associated with increases in the mRNA content for both peroxisome proliferator-activated receptor (PPAR) \(\gamma\) and PPAR\(\delta\) in skeletal muscle. The increase in gene expression for these transcription factors was related to increases in the expression of several genes involved in fatty acid transport, activation, and oxidation. Tumor burden also resulted in increases in PPAR\(\gamma\) coactivator-1\(\alpha\) gene expression and pyruvate dehydrogenase kinase 4. All these changes in lipid metabolism genes suggest that a metabolic shift occurs in skeletal muscle of tumor-bearing rats toward a more oxidative phenotype. Formoterol treatment to tumor-bearing rats resulted in an amelioration of all the changes observed as a result of tumor burden. Administration of this \(\beta_2\)-adrenergic agonist also resulted in a decrease in mRNA content of muscle PPAR\(\alpha\), PPAR\(\delta\), and PPAR\(\gamma\), as well as in mRNA levels of many of the genes involved in both lipid and mitochondrial metabolism. All these results suggest an involvement of the different PPARs as transcription factors related with muscle wasting and also indicate that a possible mode of action of the anticaehtic compound formoterol may involve a normalization of the levels of these transcription factors. [Cancer Res 2007;67(13):6512–9]

Introduction

Muscle wasting is a common feature in many pathologic states, including infection and cancer (1). Muscle wasting, the main trend of cachexia, is responsible for the death of at least 30% of cancer patients (2). Although we know the main events related with muscle wasting [activation of myofibrillar protein degradation, induction of apoptosis, and activation of uncoupling proteins (UCP); refs. 3, 4], we have contradictory evidence about the possible mediators involved. Indeed, whereas involvement of different cytokines, mainly tumor necrosis factor-\(\alpha\) (TNF\(\alpha\)) and interleukin-6 (IL-6), has been postulated, other studies describe a more direct role for tumor-derived factors, such as proteolysis-inducing factor (PIF) and lipid-mobilizing factor (5, 6). The intracellular signaling pathway may have a key role, from a therapeutic point of view, especially if there are different mediators involved. Taking this into consideration, a lack of knowledge about signaling pathways and transcription factors involved in muscle wasting exists. Some work has postulated a role for nuclear factor-\(\kappa\)B (NF-\(\kappa\)B) in muscle wasting associated with cytokines (7) and tumor-derived factors (8). Other transcription factors, such as activator protein-1 (AP-1) and CCAAT/enhancer binding protein (C/EBP), have also been involved in sepsis-induced muscle cachexia (9). Results from our laboratory indicate that the transcription factor AP-1 could also be involved during cancer cachexia (10, 11). Not much attention has been focused on the role of peroxisome proliferator-activated receptors (PPAR) in skeletal muscle. These transcription factors are associated with changes in lipid metabolism as well as UCP expression (12) and apoptosis (13).

PPARs are transcription factors belonging to the superfamily of nuclear receptors. Three isoforms (\(\alpha\), \(\delta\), and \(\gamma\)) have been described (14). They act on DNA response elements as heterodimers with the nuclear retinoic acid receptor. Their natural activating ligands are fatty acids and lipid-derived substrates. PPAR\(\alpha\) is present in liver, heart, and, to a lesser extent, skeletal muscle; when activated, it promotes fatty acid oxidation, ketone body synthesis, and glucose sparing. PPAR\(\gamma\) is expressed in adipose tissue, lower intestine, skeletal muscle, and immune cells; activation of PPAR\(\gamma\) induces the differentiation of preadipocytes into adipocytes and stimulates triglyceride storage. The PPARs are thus major regulators of lipid and glucose metabolism, allowing adaptation to the prevailing nutritional environment (14). PPAR\(\delta\) has a broad expression pattern in adult and is expressed very early during embryogenesis (15). These past few years, it has been shown that treatment with PPAR\(\delta\) agonists normalizes blood lipids and also reduces insulin resistance and adiposity in rodents and primates. Utilization of both cellular and animal models revealed that this nuclear receptor plays a central role in the control of fatty acid burning in adipose tissue and skeletal muscle. Furthermore, PPAR\(\delta\) seemed to be important for adaptive response of skeletal muscle to environmental changes, such as physical exercise (15).

\(\beta_2\)-adrenergic agonists are potent muscle growth promoters in many animal species (16, 17), resulting in skeletal muscle hypertrophy (18–20) and reducing body fat content (21, 22). Interestingly, results from our laboratory clearly indicate that formoterol is a very efficient agent preventing muscle weight loss in tumor-bearing rats (23). In \textit{vivo} treatment can effectively reverse muscle wasting loss decreasing protein degradation and increasing the rate of protein synthesis in skeletal muscle, therefore favoring protein accretion (23).

Bearing this in mind, the aim of the present investigation was to ascertain if tumor burden induces any changes in PPARs gene transcription in skeletal muscle and if these changes are associated...
with alterations in gene transcription of different types of proteins involved in lipid metabolism. A second objective in the present investigation was to see if these changes could be reversed by administration of the β2-agonist formoterol, a molecule that shows a clear anticaclhectic action in skeletal muscle during cancer (23).

Materials and Methods

Animals. Male Wistar rats (Interfauna) of 5 weeks of age were used. The animals were maintained at 22 ± 2°C with a regular light-dark cycle (light on, 08:00–20:00) and had free access to food and water. The food intake was measured daily. All animal manipulations were made in accordance with the European Community guidelines for the use of laboratory animals.

Tumor inoculation and treatment. Rats were divided into two groups, namely controls and tumor hosts. The latter received an i.p. inoculum of the corresponding volume of solvent. On day 7 after tumor transplantation, the animals were weighed and anesthetized with an i.p. injection of ketamine 80 mg/kg and xylazine 10 mg/kg (Sigma). The tumor fraction was obtained: the pellets being resuspended in 500 μL of a protease inhibitor cocktail/mL of buffer. They were then centrifuged at 7,000 rpm for 5 min at 4°C, and the supernatants were collected. About FATanalysis, an enriched plasma membrane was obtained by density centrifugation at 47,000 rpm for 1 h at 4°C. Protein concentrations were determined according to the method of Lowry et al. (26).

RNA isolation. Total RNA from soleus and extensor digitorum longus (EDL) muscle was extracted by TriPure kit (Roche), a commercial modification of the acid guanidinium isothiocyanate/phenol/chloroform method (25).

Real-time PCR. First-strand cDNA was synthesized from total RNA with oligonucleotide dT15 primers and random primers p(dN)6 by using a reverse transcriptase kit (Transcriptor Reverse Transcriptase, Roche). Analysis of mRNA levels for PPARα, PPARβ, PPARγ, muscle carnitine palmitoyltransferase-I (MCPTI), and PTPII were done with primers designed to detect gene expression in the exponential phase (24). Both groups were further divided into treated and untreated, the former being given daily i.p. dose of formoterol (0.3 mg/kg body weight), dissolved in physiologic solution, and the latter a corresponding volume of solvent. On day 7 after tumor transplantation, the animals were weighed and anesthetized with an i.p. injection of ketamine/xylazine mixture (3:1; Imalgene and Rompun, respectively). The tumor was harvested from the peritoneal cavity and its volume and cellularity were evaluated. Tissues were rapidly excised, weighed, and frozen in liquid nitrogen.

Biochemicals. They were all reagent grade and obtained either from Roche S.A. or from Sigma Chemical Co.

Table 1. Food intake, body weight, and muscle weight in tumor-bearing rats

<table>
<thead>
<tr>
<th>Experimental groups</th>
<th>C, n (mean ± SE)</th>
<th>C + F, n (mean ± SE)</th>
<th>TB, n (mean ± SE)</th>
<th>TB + F, n (mean ± SE)</th>
<th>P, ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBW-FBW</td>
<td>5 (49 ± 3%)</td>
<td>5 (50 ± 2%)</td>
<td>6 (11 ± 3%)</td>
<td>7 (17 ± 3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Food intake</td>
<td>5 (133 ± 11)</td>
<td>5 (131 ± 23)</td>
<td>6 (106 ± 13)</td>
<td>7 (108 ± 13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Muscle weights</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSN</td>
<td>5 (718 ± 10.5)</td>
<td>4 (774 ± 8)</td>
<td>5 (505 ± 17)</td>
<td>7 (611 ± 18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Soleus</td>
<td>5 (52 ± 2.2)</td>
<td>4 (52 ± 1.6)</td>
<td>5 (41 ± 2.7)</td>
<td>6 (44 ± 1.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>EDL</td>
<td>5 (59 ± 2)</td>
<td>5 (60 ± 1.6)</td>
<td>5 (42 ± 1.8)</td>
<td>6 (51 ± 2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tibialis</td>
<td>5 (236 ± 1.5)</td>
<td>5 (266 ± 4.5)</td>
<td>5 (171 ± 4.8)</td>
<td>7 (200 ± 9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NOTE: For further details, see Materials and Materials. n is the number of animals. Food intake (grams) refers to the ingestion for each rat during the period of the experiment before sacrifice (7 d). Initial body weight-final body weight without tumor is expressed as grams. Tissue weights are expressed as mg/100 g of initial body weight. Formoterol was given for 7 d s.c. (0.3 mg/kg body weight). Statistical significance of the results by one-way ANOVA and statistically significant difference by post-hoc Duncan test. Different superscripts indicate differences between groups.

Abbreviations: IBW, initial body weight; FBW, final body weight without tumor; GSN, gastrocnemius; C, control; F, formoterol-treated animals; TB, tumor-bearing animals.

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(Bio-Rad) were used as secondary antibodies. The membrane-bound immune complexes were detected by an enhanced chemiluminescence system (EZ-ECL).

**Statistical analysis.** Statistical analysis of the data was done by means of one-way ANOVA.

**Results and Discussion**

Muscle wasting during different pathologic conditions exerts a negative effect on survival and quality of life in the patient. Therefore, understanding the molecular mechanisms and the different mediators involved provides for the design of efficient therapeutic approaches (28). From this point of view, the therapy against wasting during cachexia has concentrated on either increasing food intake or normalizing the persistent metabolic alterations that take place in the patient. It is difficult to apply a therapeutic approach based on the neutralization of the potential mediators involved in muscle wasting (i.e., TNF-α, IL-6, IFN-γ, and PIF) because many of them are involved at the same time in promoting the metabolic alterations and the anorexia present in the cancer patients (29). Bearing this in mind, it is obvious that a good understanding of the molecular mechanisms involved in the signaling of these mediators may be very positive in the design of the therapeutic strategy. This is especially relevant because different mediators may be sharing the same signaling pathways (30, 31). However, very few investigations have focused on the signaling of these mediators in skeletal muscle, especially about transcription factors. Penner et al. (32) described, in a model of sepsis, the involvement of NF-κB and AP-1 in muscle wasting. Other reports, using experimental cancer models, have also suggested that NF-κB is involved in the signaling of muscle wasting (30, 31). In our own laboratory, we have shown recently that there is an increased activation of AP-1 in skeletal muscle of tumor-bearing rats, therefore suggesting that this factor is indeed involved in the muscle events that take place during cancer cachexia (10). Indeed, the i.m. administration of adenosviruses carrying TAM-67 [a negative-dominant of c-jun (AP-1)] resulted in an improvement of the muscle weight during tumor growth (11).

<table>
<thead>
<tr>
<th>Table 2. Gene expression of different proteins related to lipid metabolism</th>
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<tbody>
<tr>
<td><strong>Experimental groups</strong></td>
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<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>(A) Skeletal muscle mRNA content of the different PPARs</strong></td>
</tr>
<tr>
<td>PPARα</td>
</tr>
<tr>
<td>EDL 4 (100 ± 13a)</td>
</tr>
<tr>
<td>Soleus 4 (100 ± 24ab)</td>
</tr>
<tr>
<td><strong>(B) Skeletal muscle mRNA content of the different genes related to lipid metabolism</strong></td>
</tr>
<tr>
<td><strong>Fatty acid transport and activation</strong></td>
</tr>
<tr>
<td>FAT 4 (100 ± 18a)</td>
</tr>
<tr>
<td>Soleus 4 (100 ± 6ab)</td>
</tr>
<tr>
<td><strong>Oxidation</strong></td>
</tr>
<tr>
<td>MCPTI 4 (100 ± 11a)</td>
</tr>
<tr>
<td>Respiratory</td>
</tr>
<tr>
<td>FAC 8 (100 ± 12a)</td>
</tr>
<tr>
<td>Soleus 4 (100 ± 5a)</td>
</tr>
</tbody>
</table>

**Note:** For further details, see Materials and Methods. n is the number of animals. The results are expressed as a percentage of controls. Statistical significance of the results by one-way ANOVA and statistically significant difference by post-hoc Duncan test. Different superscripts indicate differences between groups.

Abbreviations: C, control; F, formoterol-treated animals; TB, tumor-bearing animals; FAT, fatty acid translocase; PPAR, peroxisome proliferator-activated receptor; FATP, fatty acid transport protein; ACS4, acyl-CoA synthetase 4; MCPTI, muscle carnitine palmitoyltransferase I; CPTII, carnitine palmitoyltransferase II.
In spite of the involvement of PPARs in several metabolic pathways that are altered during cancer cachexia, no information is available on the mRNA levels of these transcription factors in skeletal muscle during this catabolic situation. This was the aim of the present investigation: to elucidate any changes of PPARs in skeletal muscle during tumor growth and also to relate them to the changes of mRNA content of different genes involved in lipid metabolism.

Table 3. Skeletal muscle protein content of different proteins related to lipid metabolism

<table>
<thead>
<tr>
<th>Experimental groups</th>
<th>C, n (mean ± SE)</th>
<th>C + F, n (mean ± SE)</th>
<th>TB, n (mean ± SE)</th>
<th>TB + F, n (mean ± SE)</th>
<th>P, ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAT</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>EDL</td>
<td>4 (100 ± 14ab)</td>
<td>6 (99 ± 17ab)</td>
<td>3 (198 ± 97b)</td>
<td>3 (66 ± 12b)</td>
<td>ns</td>
</tr>
<tr>
<td>Soleus</td>
<td>5 (100 ± 5c)</td>
<td>7 (108 ± 17c)</td>
<td>5 (160 ± 25c)</td>
<td>3 (99 ± 18c)</td>
<td>0.09</td>
</tr>
<tr>
<td>MCPTI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDL</td>
<td>5 (100 ± 7ab)</td>
<td>6 (38 ± 14b)</td>
<td>5 (256 ± 93b)</td>
<td>3 (97 ± 12ab)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Soleus</td>
<td>4 (100 ± 16c)</td>
<td>7 (94 ± 22c)</td>
<td>5 (319 ± 50c)</td>
<td>4 (185 ± 35c)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PDK4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDL</td>
<td>4 (100 ± 16c)</td>
<td>4 (77 ± 6c)</td>
<td>3 (175 ± 21bc)</td>
<td>4 (99 ± 29bc)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Soleus</td>
<td>5 (100 ± 20)</td>
<td>6 (109 ± 13c)</td>
<td>3 (170 ± 31c)</td>
<td>4 (135 ± 55c)</td>
<td>ns</td>
</tr>
<tr>
<td>PGClα</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDL</td>
<td>5 (100 ± 11c)</td>
<td>6 (92 ± 13c)</td>
<td>4 (341 ± 83bc)</td>
<td>4 (131 ± 20bc)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Soleus</td>
<td>4 (100 ± 9c)</td>
<td>7 (64 ± 9c)</td>
<td>4 (196 ± 26bc)</td>
<td>3 (95 ± 21bc)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NOTE: For further details, see Materials and Methods. n is the number of animals. The results are expressed as a percentage of controls. Statistical significance of the results by one-way ANOVA and statistically significant difference by post-hoc Duncan test. Different superscripts indicate differences between groups.

Abbreviations: C, control; F, formoterol-treated animals; TB, tumor-bearing animals; FAT, fatty acid translocase; MCPTI, muscle carnitine palmitoyltransferase I; PDK4, pyruvate dehydrogenase kinase-4; PGClα, PPAR coactivator-1α; ns, nonsignificant differences.

Table 1 shows the effect of tumor growth on body weight, food intake, and muscle weights in animals bearing the Yoshida AH-130 ascites hepatoma. The growth of this tumor causes in the host a rapid and progressive loss of body weight and tissue waste, particularly in skeletal muscle (33). Acceleration of tissue protein breakdown accounts for most of the waste in the AH-130 bearers (24, 34). The effects of the tumor on weight loss were very

Figure 1. A, skeletal muscle protein content of mitochondrial complex II. Porin was used as invariant control. B, soleus mRNA content of the different MHCs. 18S was used as invariant control. For further details, see Materials and Methods. Columns, mean of four animals in each group; bars, SE. The results are expressed as a percentage of controls. C, control; F, formoterol-treated animals; TB, tumor-bearing animals. Statistical significance of the results by one-way ANOVA and statistically significant difference by post-hoc Duncan test. a, b, and c, differences between groups.
significant, with a decrease of 28% in the tumor-bearing group. This effect on body weight was accompanied by a marked anorexia: the tumor-bearing rats ate 20% less than the control ones (Table 1). It can also be seen that the implantation of the tumor resulted in a general decrease of muscle weights (30% gastrocnemius, 29% EDL, 28% tibialis, and 21% soleus) 7 days after the inoculation of the tumor. These changes were associated with increases in the mRNA content for PPARγ (48% in EDL and 208% in soleus) and PPARδ (141% in EDL and 376% in soleus) but no changes in PPARα mRNA content (Table 2A). It is interesting to note here that PPARδ is especially important for adaptable response in skeletal muscle and precisely the largest changes occur at the level of this transcription factor (15). The increase in gene expression for these two transcription factors was related with increases in the expression of genes involved in fatty acid transport activation and oxidation. Thus, FAT and FATP (both proteins associated with fatty acid cellular transport) were increased 215% and 51% in EDL and 86% and 81% in soleus, respectively (Table 2B). In addition, FAT protein content was also increased in soleus (60%) of tumor-bearing animals (Table 3). Similarly ACS4 (the protein that activates the intracellular fatty acids for their subsequent use in oxidation pathways) was increased 38% in soleus (Table 2B). Finally, MCPT1 and CPTII mRNA content (both involved in the transport of fatty acid across the mitochondrial membrane) were also increased as a result of tumor burden by 153% and 116% for MCPT1 in EDL and soleus, respectively, and 88% and 56% for CPTII in EDL and soleus, respectively. MCPT1 protein content was also increased in EDL (156%) and in soleus (219%) muscles of tumor-bearing animals (Table 3). All these results agree with previous reports that have already suggested that lipid metabolism is increased in skeletal muscle of tumor-bearing rats (35). In addition, all these changes in lipid metabolism genes clearly suggest that a metabolic shift occurs in skeletal muscle of tumor-bearing rats toward a more oxidative phenotype. Previous studies have shown that PPARδ is involved in muscle fiber composition; an increase in this transcription factor determines a more oxidative fiber phenotype (36). Bearing this in mind, the results found in this study clearly agree with this previously reported data. In fact, as can be seen in Fig. 1A, tumor burden resulted in a clear increase (49%) in oxidative muscle fibers, as measured by the expression of the MHCI gene (27). Conversely, the presence of the tumor did not have any effects on the mRNA content of MHCIIA, a clear glycolytic marker (Fig. 1A; ref. 27). The same tendency toward a more oxidative phenotype in the muscles of tumor-bearing rats was confirmed when analyzing the mitochondrial complex II protein content as observed in Fig. 1B (37). PGC1α is a transcriptional coregulator that coordinates the formation/maintenance of slow twitch fibers in skeletal myocytes, and this seems to be directly controlled by PPARδ (37). In addition, PPARs seem to independently regulate specific PDK isoforms transcript levels, which are likely to impart important metabolic mediation of fuel utilization by the muscle. Experiments to date suggest that PDK4 is the major isoenzyme responsible for changes in pyruvate dehydrogenase complex activity in response to various different metabolic conditions (38). Tumor burden also resulted in increases in the PGC1α gene expression (83% and 102% in EDL and soleus, respectively) and PDK4 (373% and 172% in EDL and soleus, respectively; Fig. 2). In addition PDK4 and PGC1α protein content was also increased both in EDL (75% and 241%, respectively) and in soleus (70% and 96%, respectively) muscles of tumor-bearing animals (Table 3). These data agree
with the work by Puigserver et al. (39) that stated that cytokine-induced activation of PGC1α in culture muscle cells or muscle in vivo causes increased respiration and expression of genes linked to mitochondrial uncoupling and energy expenditure. It is therefore possible to suggest that the cytokine changes related with cancer cachexia are altering the mRNA content of PGC1α and this may affect the transcriptional activity of both PPARγ and PPARδ. In connection with this, it is interesting to remark that the activation of UCP2 and UCP3 is also observed in tumor-bearing rats (40). This could be very well linked with PPARs activation, possibly through PGC1α coactivation.

Formoterol, a β2-adrenergic agonist, is a very efficient agent preventing muscle weight loss in tumor-bearing rats (23). Bearing this in mind, we decided to see if the effects of formoterol on muscle wasting during experimental tumor growth were connected with changes in PPARs and the genes involved in lipid metabolism studied above. The results obtained seem to indicate that formoterol treatment can normalize the changes induced by the tumor (Fig. 2; Tables 1–3). Several studies have shown that β2-adrenergic agonists act on skeletal muscle by changing the fiber composition toward a more glycolytic pattern (41). Taking this into account, the different effects of formoterol on different types of muscles were studied; therefore, these studies were done in a predominantly oxidative muscle (soleus) and in a predominantly glycolytic muscle (EDL). The results found here are in line with previously described observations (41). As seen in Fig. 1A, formoterol treatment resulted in a significant increase in MHCIIA (a glycolytic marker) in mRNA soleus content, in both control and tumor-bearing animals. In addition, formoterol also significantly decreased mitochondrial complex II content in tumor-bearing rats (Fig. 1B), this observation supporting further the change in fiber composition.

It is interesting to note that formoterol also had an effect on nontumor-bearing animals (Table 3A and B), therefore suggesting that the action [possibly linked with variations of the intracellular concentration of cyclic AMP (cAMP) in cells] may be linked with changes in PPARs (42, 43). In fact, a previous report using the β2-agonist phenylephrine already suggests this possibility (44). On the other hand, it is well known that β2-agonists also affect lipid metabolism on adipose tissue, decreasing lipid synthesis and favoring lipid oxidation (45), but this is the first report that clearly shows a possible action of β2-agonists on skeletal muscle lipid metabolism. The effects of the β2-agonists via β2-adrenergic receptors increase cAMP and interfere with PPARs gene expression (Fig. 3). However, another possibility is that formoterol actually interferes with the signaling of TNFα on skeletal muscle cells. Indeed, a report already suggests that the β2-agonist clenbuterol decreases the circulating levels and activity of TNFα (46). This makes particular sense for the tumor model involved in this study because the Yoshida AH-130 ascites hepatoma seems to be highly dependent on the increase of TNFα circulating levels (47). In addition, in this study, formoterol treatment also reduced the TNFα mRNA content in gastrocnemius muscle [tumor, 185 ± 15a arbitrary units (4); tumor treated with formoterol, 115 ± 9b arbitrary units (3); P < 0.05]. (Statistical significance of the results by one-way ANOVA and statistically significant difference by post-hoc Duncan test; different superscripts indicate differences between groups).

The data presented here, in a way, complicate the understanding of the different transcription factors in muscle wasting because some reports have suggested that activation of different PPARs may be useful in preventing metabolic alterations linked with inflammation by cytokines (48). However, other reports suggest the opposite, emphasizing that PPARs may have a role in mediating

Figure 3. Hypothetical involvement of the different transcription factors during muscle wasting in cancer cachexia. ARβ2, β2-adrenoceptor; IL-6R, IL-6 receptor; PIFR, PIF receptor; TNFR1, TNF receptor 1; TNFR2, TNF receptor 2.
cytokine action in skeletal muscle (39). In addition, several studies (49) indicate that PPARs can partially interfere in NF-κB signaling in skeletal muscle, therefore controlling to some extent the action exerted by cytokines through these transcription factors (Fig. 3). Bearing all this in mind, one has to look at the plethora of transcription factors involved in muscle wasting during cancer cachexia because possibly some of them play a more important role in some cases, depending on the species, the tumor model, and the tumor stage. It is perfectly conceivable to understand that by agonizing PPARα and PPARβ, one can produce a reduction in muscle weight partly through the interference in the NF-κB signaling system. It can also be suggested that the elevation of the different PPARs during muscle wasting in cancer may be a counter metabolism triggered by the host to control an excessive degradation of muscle protein and favoring lipid utilization for muscle.

In conclusion, the results presented here contribute to a better understanding of the role of transcription factors in the muscle tissue during cancer cachexia. It becomes clear that future research into this field is necessary and may provide important tools for designing effective drugs for the treatment of wasting in skeletal muscle during pathologic conditions.

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References


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