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Inactivating STAT3: bad for tumor, good for muscle

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The Signal Transducer and Activator of Transcription 3, also known as STAT3, is a transcription factor originally identified as downstream effector of IL6-, IFNγ- and IFNα-mediated inflammatory pathways, and it is undesirably activated in multiple types of cancer.[1] STAT3 plays a role in tumor cell proliferation, survival, angiogenesis, metastasis and immune responses. As a consequence, an active research to inhibit STAT3 and generate anti-tumor effects is underway. Unfortunately, the high complexity of the signaling cascades wherein STAT3 is interdigitated hardens the possibility of selectively inhibiting cancer growth without deleterious side effects (i.e. immunosuppression). Upstream activators of STAT3, as the Janus Tyrosine Kinase (JAK), are therefore regarded as better inhibitory targets also because STAT3 lacks its own enzimatic activity, a preferential pre-requisite for drug targets. Interestingly, recent studies have recognized Toll-like receptors (i.e. TLR4) as well as G-protein-coupled receptors (i.e. S1PR1) as additional activators of the JAK/STAT3 pathway, thus pointing to new directions for targeting STAT3 in cancer.

Systemic chronic inflammation not only promotes and sustains cancer growth, but also the deleterious wasting of multiple tissues, including heart, bone, fat and skeletal muscle (i.e., cancer cachexia) that occurs in up to 80% of cancer patients in their advanced stages. Cachexia arises also during other cancer-free states, like congestive obstructive pulmonary diseases (COPD), diabetes, HIV infection, burns or cardiac failure through similar mechanisms (i.e. elevated plasma levels of IL6 and muscle catabolysm).[2] In particular, the rapid growth of cancerous lesions seems to cause a systemic dysmetabolism where the tumor requires more aminoacids and sugars to survive (especially glutamine and glucose, respectively) and the body promptly adapts to this undergoing wasting of multiple tissues. Since skeletal muscle is mainly constituted of proteins, it undergoes massively catabolic processes to rapidly respond to stress (i.e. cancer). During cancer cachexia, the liver undergoes gluconeogenesis starting from the aminoacids catabolized from skeletal muscles and from the glycerol provided by the fat tissue, which in turn releases non-esterified fatty acids to the tumor, responding as to a sort of undernourished state. If not stopped, this deleterious and unsustainable process can lead patients to death through cardiac or respiratory failure or general body collapse.[3]

Finding novel drugs able to break this dangerous circuitry between various organs and the tumor itself may be of great advantage extending the quality of life of cancer patients and giving them more chances to respond to long-term therapies in good shape.[2,3] Also unraveling the abilities of "old" drugs (already on the market) to break this vicious circle can be advantageous and even faster for the cure of cachectic patients because already approved by regulatory agencies. An ideal drug may be one that has suppressive effect on tumor without affecting the mass and function of muscles or alternatively, one that even if it does not delay tumor growth at least stops the systemic wasting. This is particularly challenging since the pathways governing cancer growth and post-natal muscle mass are similar (i.e. AKT-PI3K, p38-MAPK, etc.). For this reason, fatigue, muscle weakness, muscle pain or muscle atrophy are often observed as side-effects of anti-cancer agents.

In clinical trials, anti-inflammatory drugs, such as antibodies against IL6 or TNFα, have proven not to inhibit muscle wasting due to cancer growth, re-addressing the research toward more convergent downstream effectors of pro-inflammatory pathways as novel drug targets. In this regard, JAK/STAT3 pathway activation has been implied in atrophying skeletal muscles downstream of IL6 and in experimental models of cancer cachexia or renal failure, thus proposing JAK and STAT3 as novel targets for preserving muscle mass and function.[4,5] Among the mechanisms, STAT3 inhibitors seem to decrease circulating levels of myostatin, a key catabolic factor in muscle for which multiple clinical trials are currenly testing inhibitors in diverse settings of muscle wasting, including cancer cachexia.[2,5]

We reported the unexpected ability of sunitinib and sorafenib, two tyrosine kinase inhibitors affecting angiogenesis, to prevent systemic cancer cachexia both at the level of muscle and adipose tissues with a negligible effect on cancer growth in unrelated mouse models of cachexia.[6] Most relevant was the ability of sunitinib to reverse the cachectic phenotype and rescue animals from the loss of fat tissue, resulting in improved survival. Similarly, also Toledo and coworkers have recently showed that sorafenib is able to block

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wasting of muscles, fat and heart in colon adenocarcinoma-bearing mice without affecting tumor growth.[7] Of note, both studies showed that the STAT3-based signaling hyperactivated in cachectic muscles was repressed by treatment with sunitinib or sorafenib, ultimately preventing the induction of important players of accelerated muscle catabolism, as MuRF1,[6] an ubiquin-ligase implicated in myofibril breakdown and atrophy[2] or atrogin-1[7]. Also both studies fail to support a direct inhibitory effect of sunitinib and sorafenib on circulating IL6. Although the target upstream of STAT3 and the mechanism/s (e.g. myostatin inhibition) responsible for the anti-cachectic effects of sunitinib/sorafenib are far from being clear, these results support the implication of STAT3 pathways in cachectic muscles, consistently with the devolopment of STAT3 selective inhibitors able to prevent muscle wasting.[4,5]

In conclusion, targeting JAK/STAT3 offers a unique opportunity to prevent muscle atrophy and fat tissue wasting. Small molecules inhibiting STAT3 have progressed over the past several years, yet a STAT3 selective and potent drug is not yet clinically available. The challenge here is to develop inhibitors as therapeutic option for cancer patients who develop cachexia. Dual crucial targets of cancer and cancer cachexia, as STAT3, need to be identified and compounds against them shall be rapidly tested in cancer patients to provide them with multiple beneficial effects.

References

1. Yu H, et al. Nat Rev Cancer 2014; 14:736-46; PMID:25342631; http://dx.doi.org/10.1038/nrc3818
2. Cohen S, et al. Nat Rev Drug Discov 2015; 14:58-74; PMID:25549588; http://dx.doi.org/10.1038/nrd4467
3. Fearon K, et al. Nat Rev Clin Oncol 2013; 10:90-9; PMID:23207794; http://dx.doi.org/10.1038/nrclinonc.2012.209
4. Bonetto A, et al. Am J Physiol Endocrinol Metab. 2012; 303:E410-21; PMID:22669242; http://dx.doi.org/10.1152/ajpendo.00039.2012
5. Zhang L, et al. Cell Metab 2013; 18:368-79; PMID:24011072; http://dx.doi.org/10.1016/j.cmet.2013.07.012
6. Pretto F, et al. Oncotarget 2015; 6(5):3043-54; Epub ahead of print, PMID:25460504.
7. Toledo M, et al. PLoS One 2014; 9:e113931; PMID:25436606; http://dx.doi.org/10.1371/journal.pone.0113931