Rapamycin

1. **mTORC1 and mTORC2**:
    - **mTORC1**: Rapamycin is well-known for inhibiting mTORC1, which is crucial for muscle protein synthesis. mTORC1 activation involves a cascade of signals from IGF-I, PI3K, PDK1, and Akt, leading to the phosphorylation of downstream targets like 4E-BP1 and p70S6K, enhancing protein synthesis and muscle hypertrophy【source】【source】.
    - **mTORC2**: Rapamycin can also affect mTORC2, although its inhibition is less direct and occurs after prolonged exposure. mTORC2 is involved in phosphorylating Akt, which is critical for various cellular functions, including survival and metabolism【source】.
2. **FOXO1**:
    - Rapamycin indirectly impacts FOXO1 through its inhibition of mTORC2. Since mTORC2 phosphorylates Akt, reduced mTORC2 activity leads to lower Akt phosphorylation. This reduction allows FOXO1 to translocate into the nucleus and promote the expression of atrogenes like atrogin-1 and MuRF-1, leading to muscle atrophy【source】.
3. **Akt**:
    - Rapamycin decreases Akt phosphorylation by inhibiting mTORC2. This inhibition affects Akt's ability to phosphorylate and inhibit TSC2, which normally inhibits mTORC1. Reduced Akt activity thus diminishes protein synthesis and promotes protein degradation pathways【source】【source】.
4. **Myostatin**:
    - Myostatin inhibits muscle growth and its activity can be potentiated by rapamycin through the reduction of mTORC1 activity. Additionally, rapamycin-induced activation of FOXO1 can increase myostatin expression, further promoting muscle atrophy【source】.

MOTS-c

1. **mTORC1 and mTORC2**:
    - **mTORC1**: MOTS-c indirectly influences mTORC1 by modulating upstream signals that affect Akt activity, although the exact interaction between MOTS-c and mTORC1 isn't explicitly described in the provided text【source】.
    - **mTORC2**: MOTS-c increases mTORC2 activity, enhancing Akt phosphorylation. This increase in Akt activity supports various anabolic processes and cellular survival pathways【source】.
2. **FOXO1**:
    - MOTS-c inhibits FOXO1 activity by promoting its phosphorylation through enhanced Akt activity. Phosphorylated FOXO1 is excluded from the nucleus and targeted for degradation via the ubiquitin-proteasome pathway. This process reduces the expression of muscle atrophy-related genes such as myostatin and atrogin-1【source】.
3. **Akt**:

    - MOTS-c enhances Akt phosphorylation by inhibiting PTEN and increasing CK2 activity, which in turn inhibits PTEN. Elevated Akt phosphorylation (at Thr308 and Ser473) leads to greater Akt activity, which phosphorylates and inhibits FOXO1, reducing muscle atrophy signals【source】.
4. **Myostatin**:
    - MOTS-c reduces myostatin expression by inhibiting FOXO1 activity. Since FOXO1 can upregulate myostatin transcription, its inhibition by MOTS-c decreases myostatin levels, promoting muscle growth and combating muscle wasting conditions【source】.

Comparison and Contrast

- **Rapamycin** inhibits mTORC1 directly and mTORC2 indirectly, leading to reduced Akt activity and increased FOXO1 activity, which promotes muscle atrophy and increases myostatin expression.
- **MOTS-c** increases mTORC2 activity, leading to enhanced Akt phosphorylation. This activity results in the inhibition of FOXO1, reducing myostatin levels and preventing muscle atrophy.

In summary, while rapamycin tends to promote muscle atrophy through the inhibition of mTOR pathways and activation of FOXO1, MOTS-c works oppositely by enhancing Akt activity, inhibiting FOXO1, and thus supporting muscle maintenance and growth.

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MOTS-c, the Most Recent Mitochondrial Derived Peptide in Human Aging and Age-Related Diseases

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