# Effets biologiques des facteurs de croissance sur la régénération musculaire

**Xavier Bigard (MD, PhD)**
Professeur Agrégé du Val-de-Grâce
Institut de Recherche Biomédicale des Armées (IRBA)
La Tronche (Grenoble) - Brétigny/Orge - France

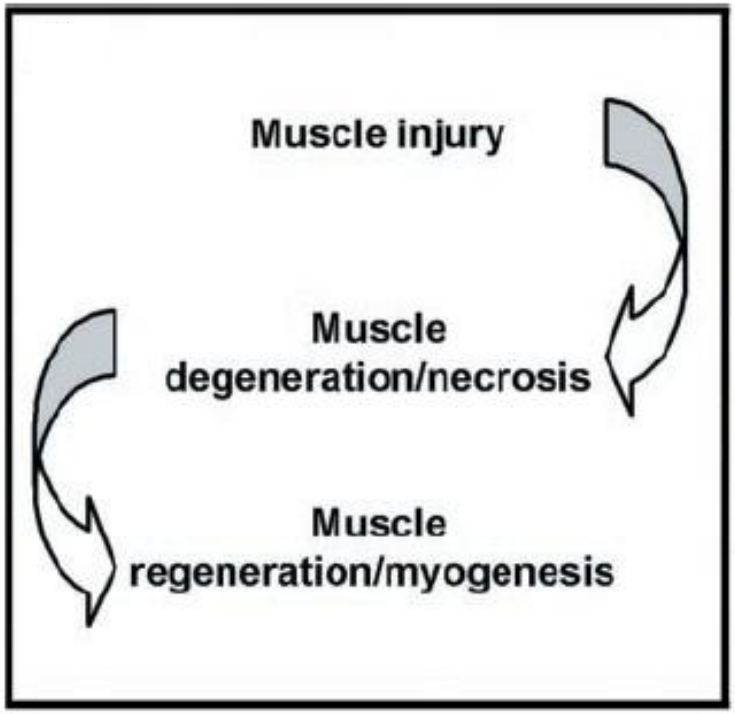
Adult skeletal muscle is highly adaptable

Skeletal muscle is susceptible to muscle injury after

- direct trauma
- acute injury ; muscular tears, strains, etc.
- intensive exercise, strain injury

A complex healing process is quickly initiated at the site of tissue damage

# Sequential events of muscle degeneration / regeneration



# Sequential events of muscle degeneration / regeneration

## 1. Degeneration

Disruption of myofiber integrity - autolysis

Inflammation

Activation

Injury

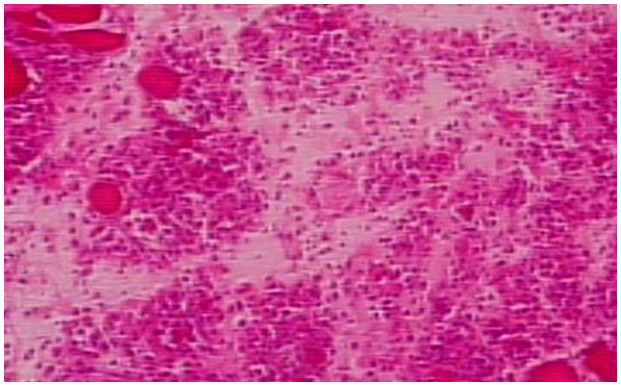
4h 8h 2days

Response of inflammatory cells (neutrophils)

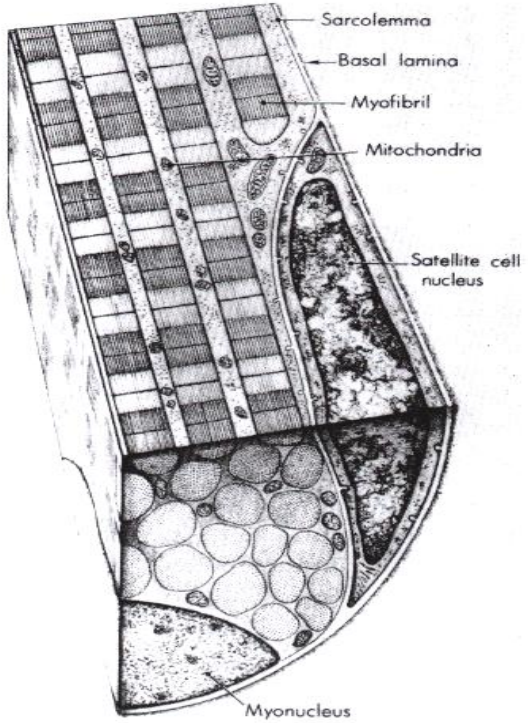
Infiltration of macrophages

Removal of cellular debris

Activation, proliferation of satellite cells



day 1 after notexin injection



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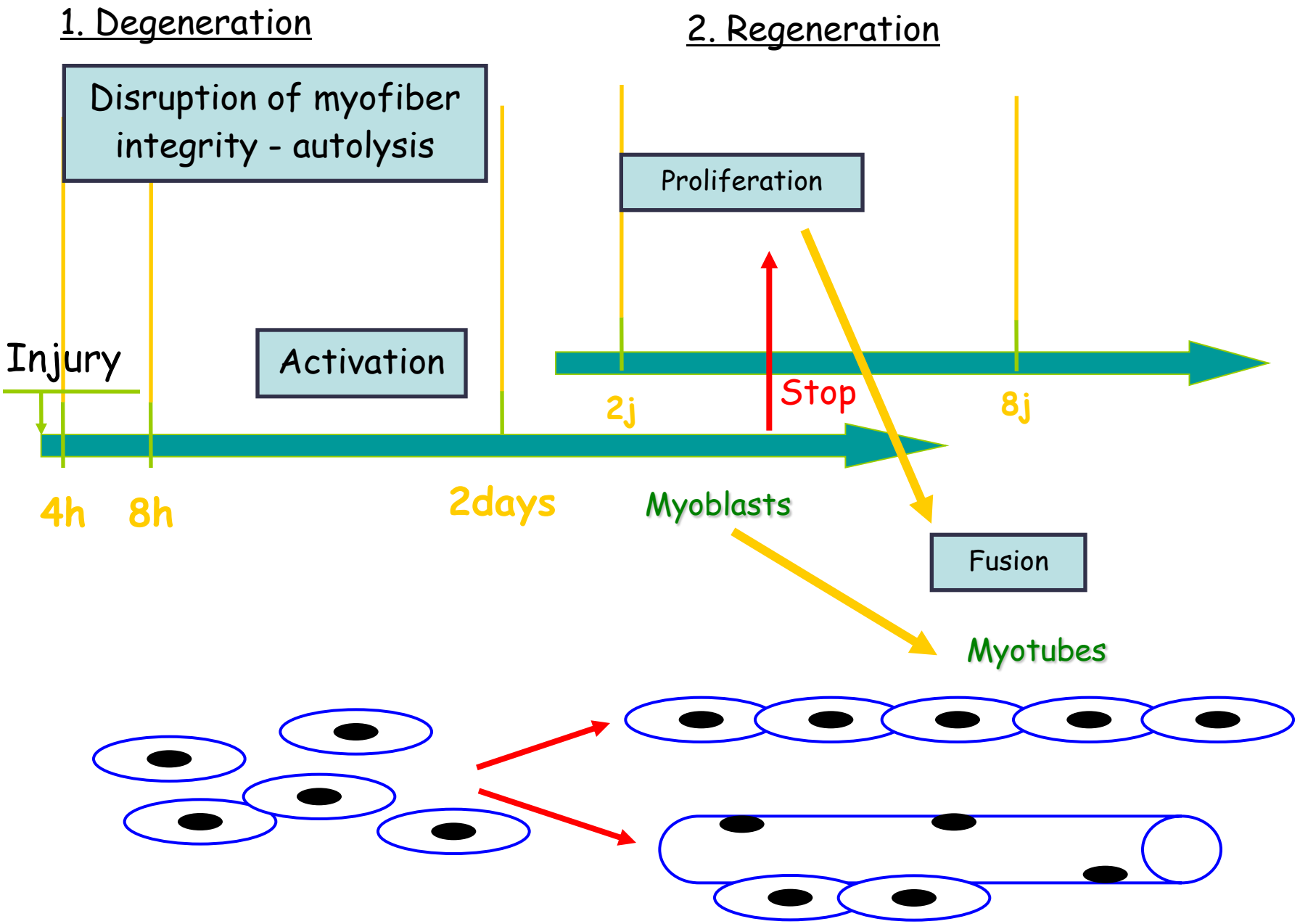


# Sequential events of muscle degeneration / regeneration

## 1. Degeneration

Disruption of myofiber integrity - autolysis

Injury

Activation

4h 8h

## 2. Regeneration

Proliferation

2j

Stop

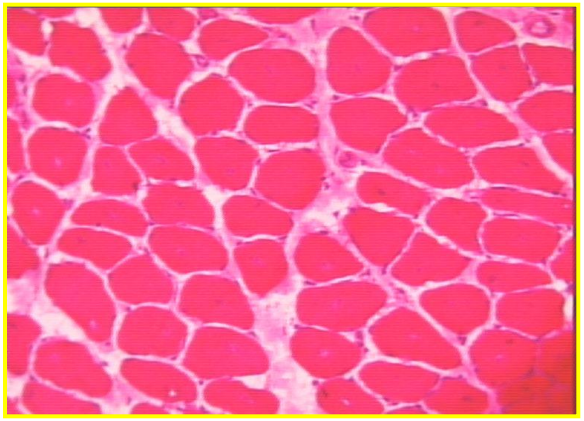
8j

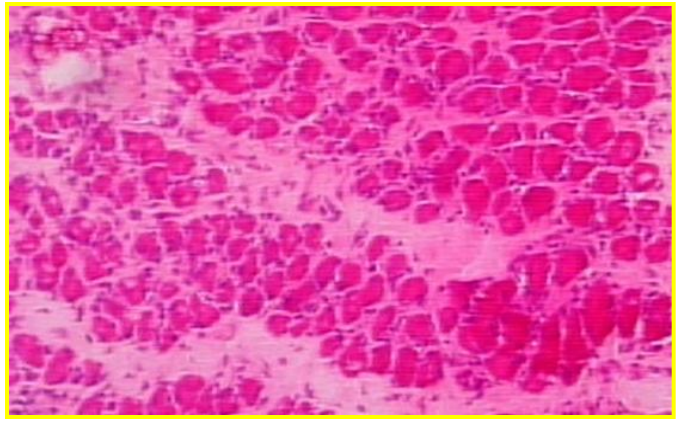
2days

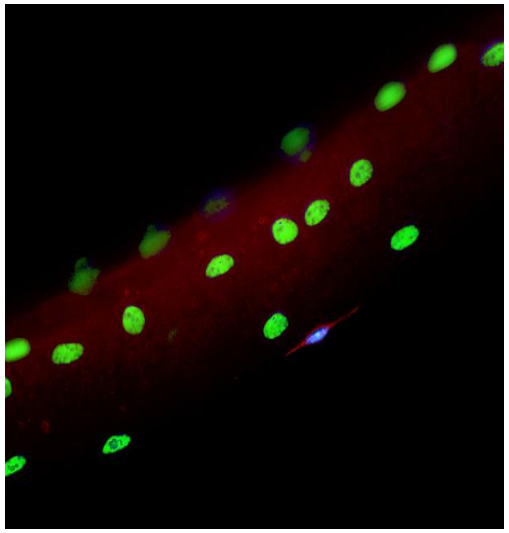
Maturation myofiber growth

Fusion

## 3. Maturation and muscle growth







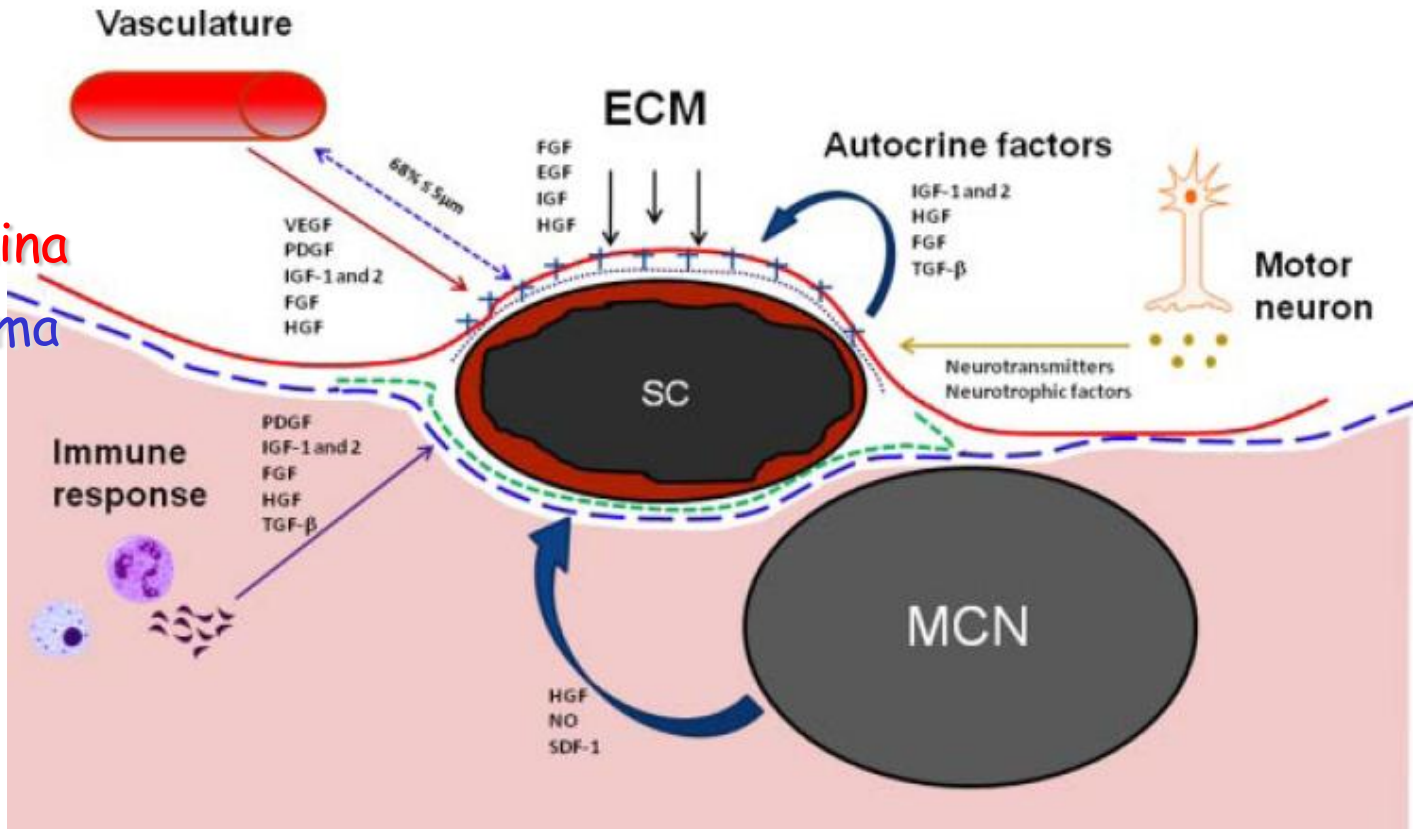
Satellite cell
activation,
proliferation and
differentiation are under the
control of growth factors released in extracellular space, from
injured myofibers
active immune cells, platelets, endothelial cells, motor neurons.

All these growth factors play a role in specific stages of muscle regeneration,

In vivo, there is a fine balance between stimulatory and inhibitory factors (++++).

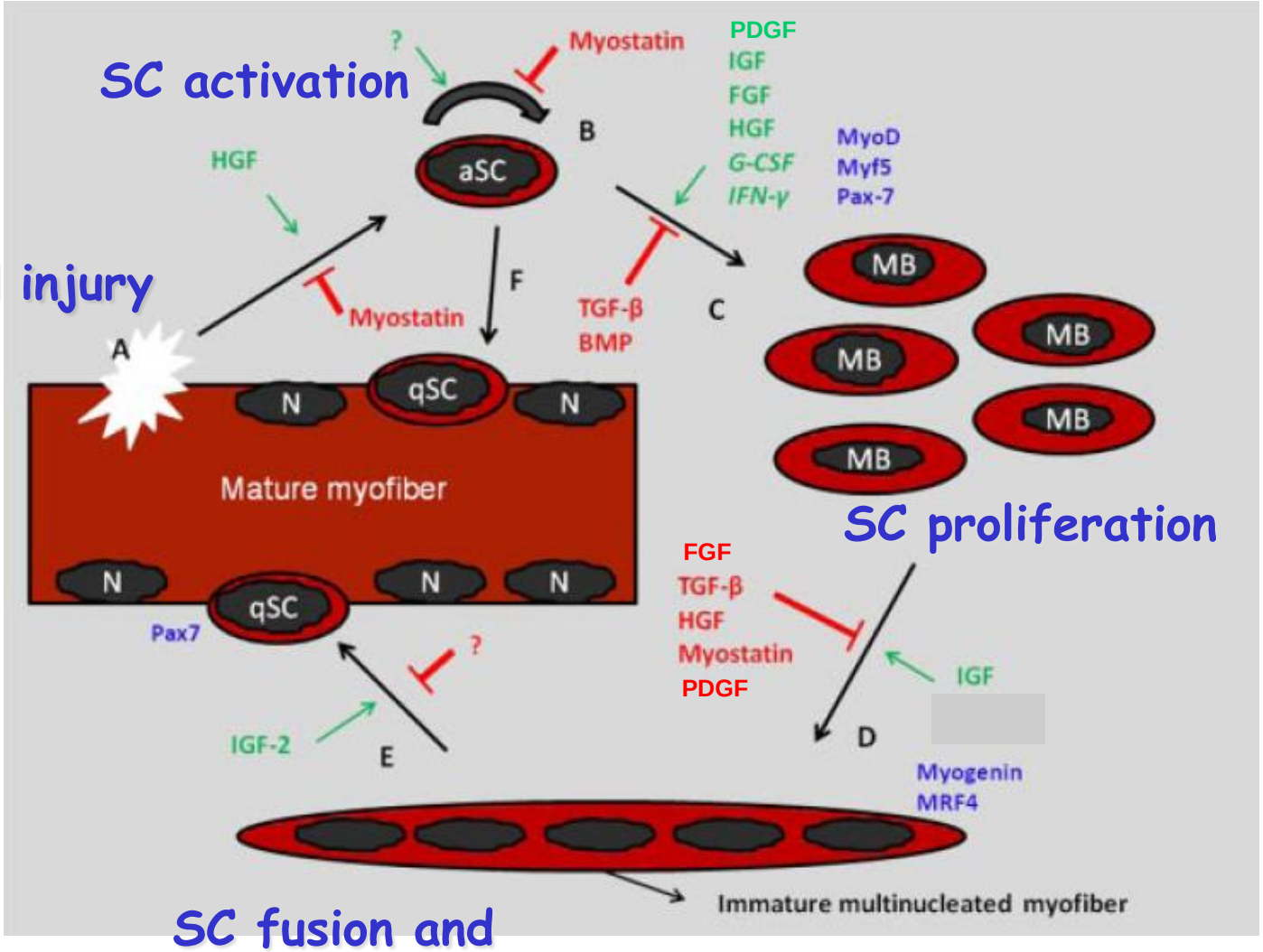
basal lamina

sarcolemma

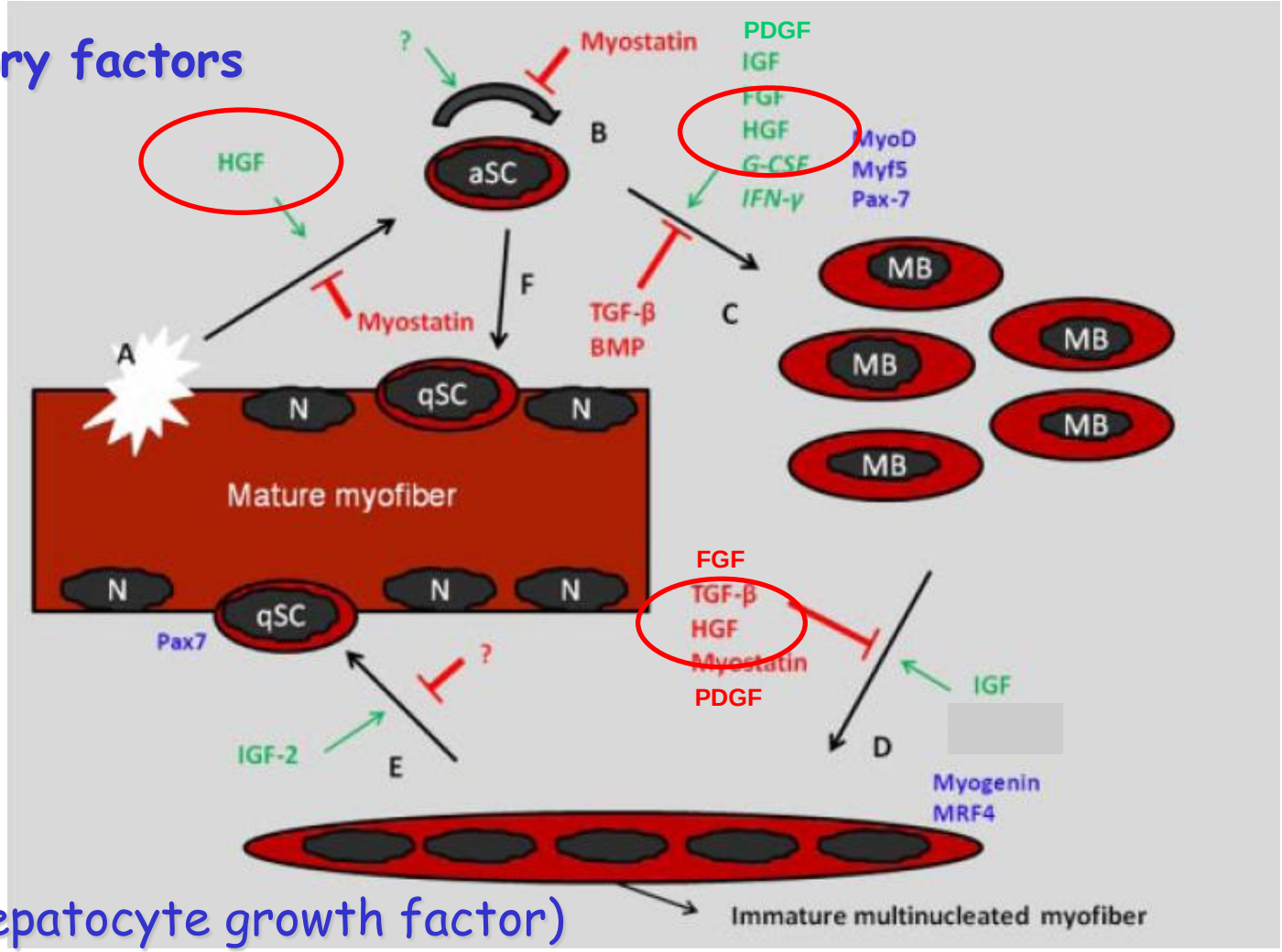



The satellite cell niche.

proximity of vessels, myonuclei and satellite cells ; strong interaction between cells through growth factors and cytokines.

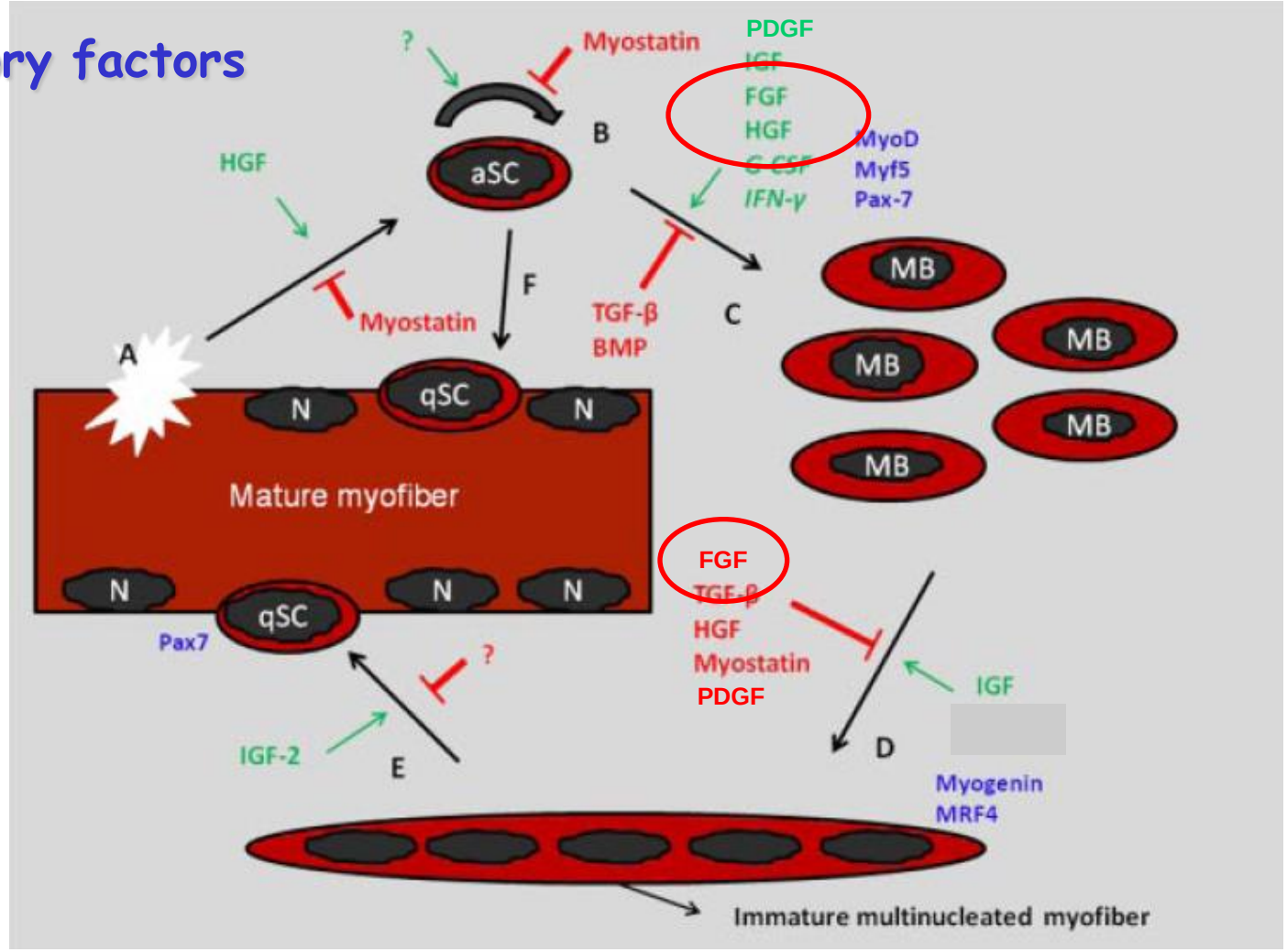

SC activation
Initial injury
SC proliferation
SC fusion and
myofiber maturation
?
Myostatin
PDGF
IGF
FGF
HGF
G-CSF
IFN-γ
MyoD
Myf5
Pax-7
HGF
B
aSC
A
Myostatin
F
TGF-β
BMP
C
MB
MB
MB
MB
MB
N
qSC
N
Mature myofiber
N
N
N
qSC
Pax7
FGF
TGF-β
HGF
Myostatin
PDGF
IGF
?
IGF-2
E
D
Myogenin
MRF4
Immature multinucleated myofiber

## stimulatory factors



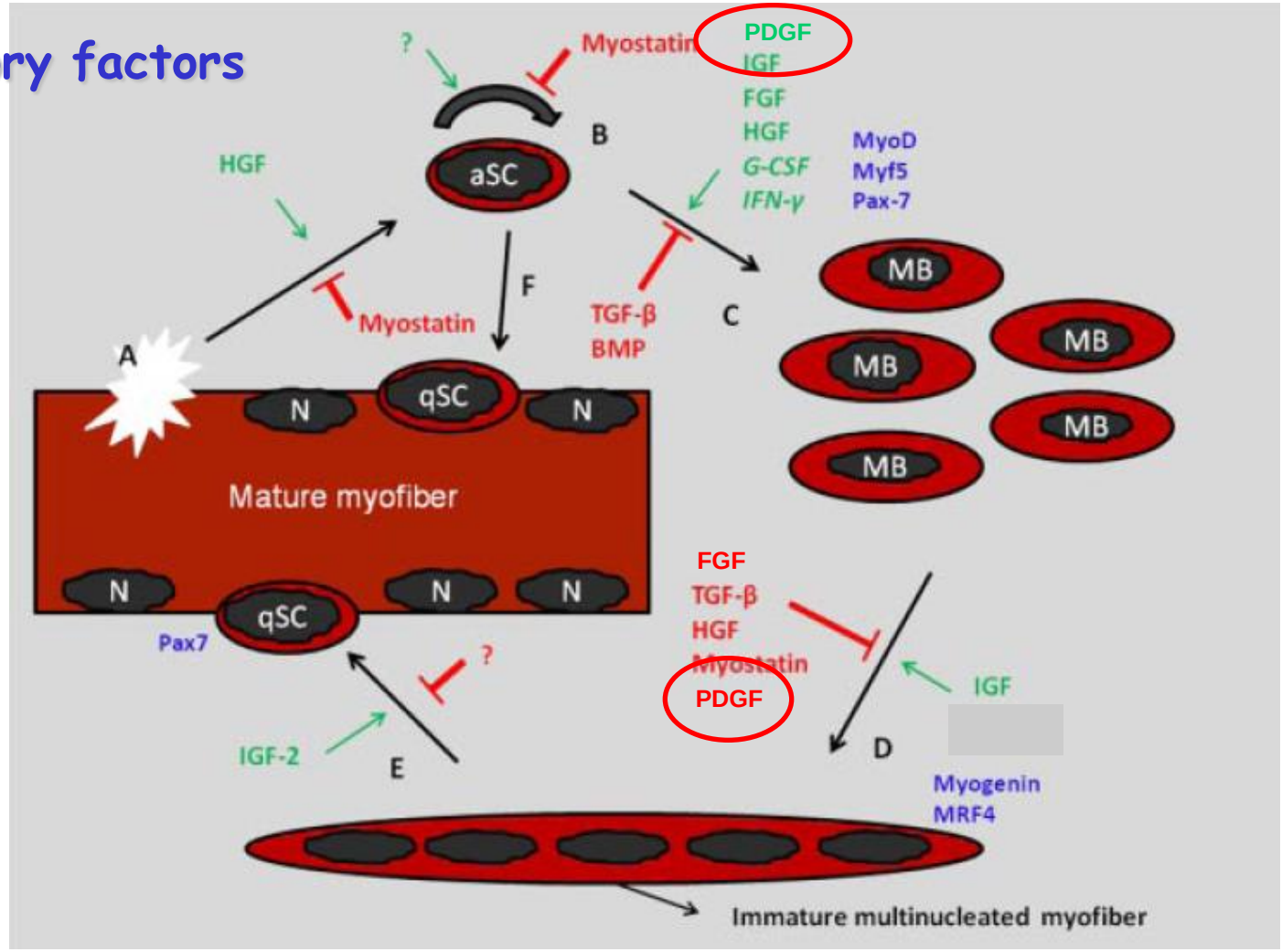

HGF (hepatocyte growth factor)
stored in the extracellular matrix,
directly released by injury, the first to activate SCs,
released after MMP expression by satellite cells (SC),
essential during the first steps of regeneration,
stimulates SC migration to the site of injury.

## stimulatory factors



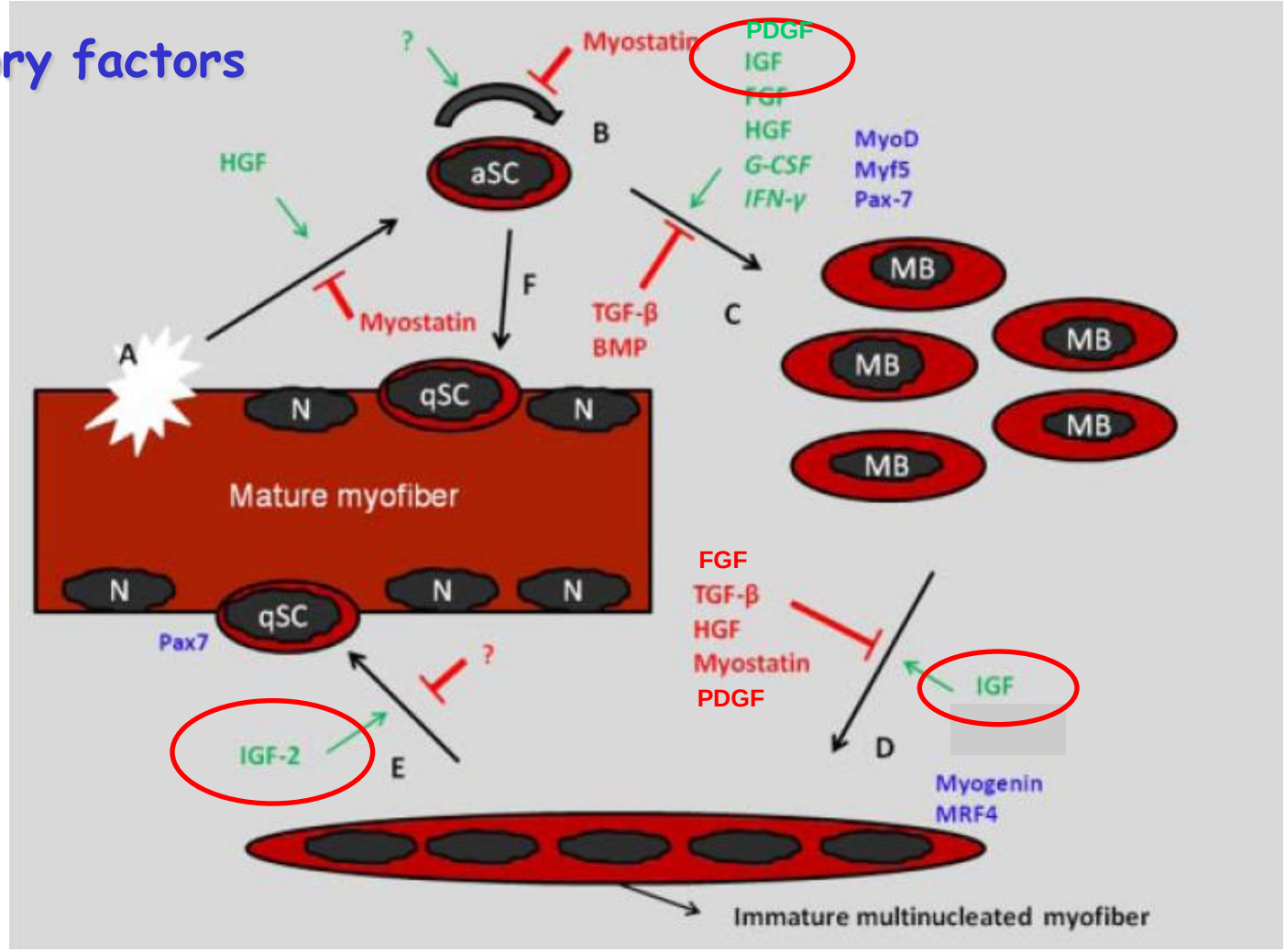

FGFs (fibrolast growth factors, FGF2, FGF6)
markedly released during the primary inflammatory response,
induces SC proliferation, and inhibits the myotube formation,
expresses genes essential for differentiation (MRFs),
key role on capillary proliferation and nerve repair.

## stimulatory factors



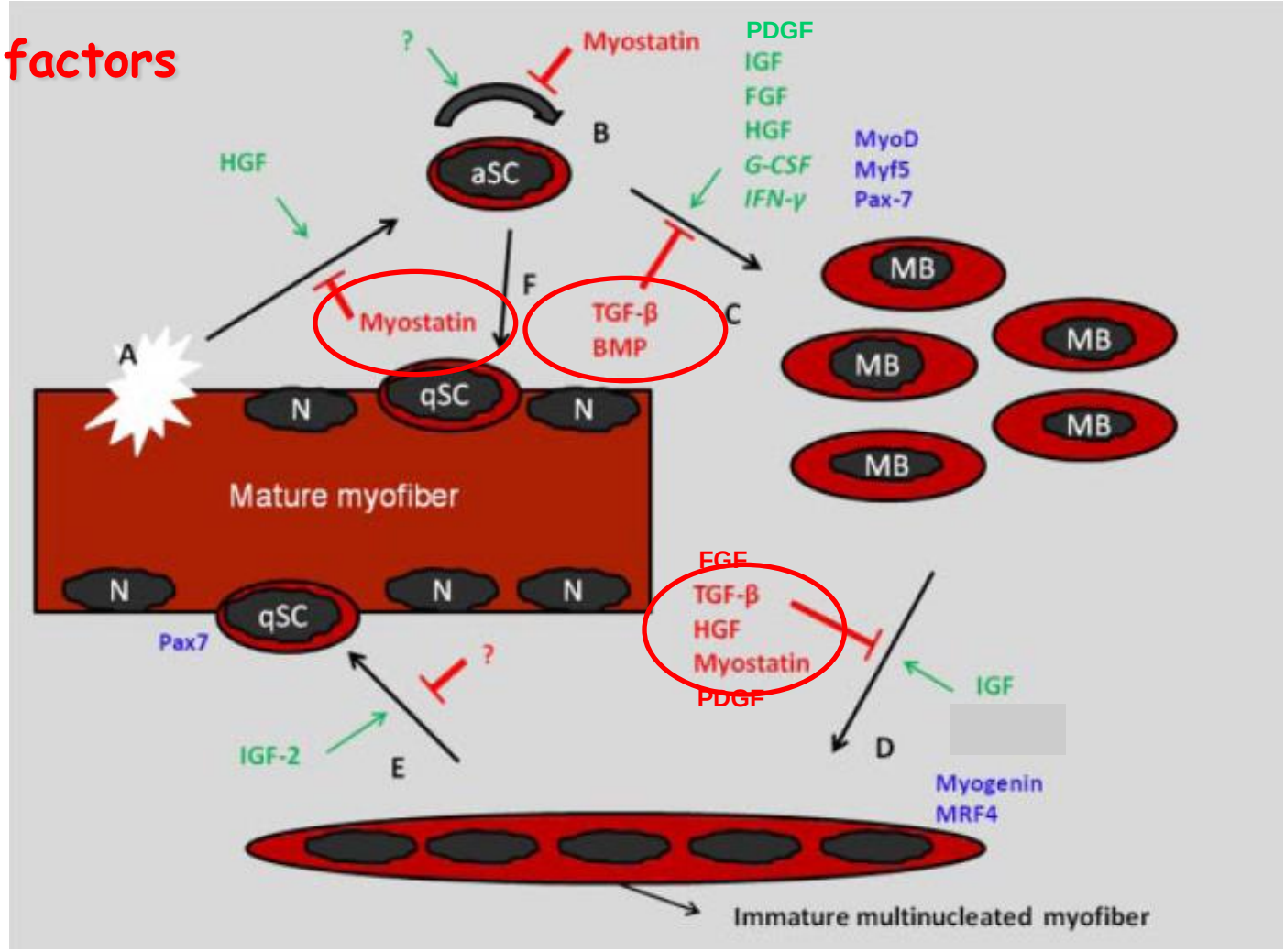

PDGFs (Platelet derived growth factor)
markedly released by degranulated platelets,
induces SC proliferation,
inhibits the terminal differentiation into myotubes.

# stimulatory factors




IGF-1 and 2,
major role in myofiber regeneration,
unique, because stimulate proliferation, differentiation and maturation.

# inibitory factors




TGFβ superfamily (TGFβ-1, -2, myostatin, etc.),
myostatin maintains SC at the quiescent state,
downregulates markers of SC activation,

## Growth factors and Platelet-Rich Plasma (PRP)

The current hypothesis is that

PRP injections deliver supraphysiological concentrations of GFs at the injured site,

influencing all cellular steps needed for myofiber regeneration,

and then enhancing muscle regeneration.

The main growth factors extracted from PRPs

HGF, b-FGF, PDGF, IGF-I and -II, VEGF, angiopoietin-1, etc.

The speed and quality of myofiber regeneration is related to the

kinetics of GF release,

GF interactions,

GF availability at the site of tissue damage.

## Growth factors and Platelet-Rich Plasma (PRP)

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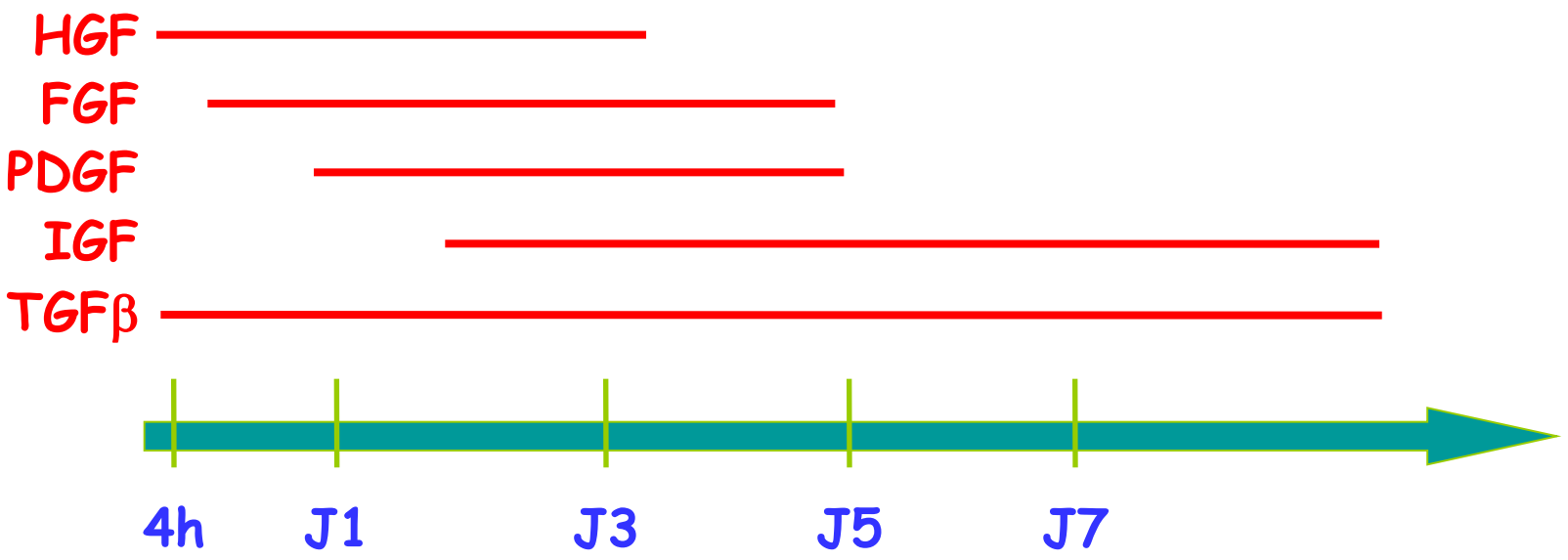


## Growth factors and Platelet-Rich Plasma (PRP)

The speed and quality of myofiber regeneration is related to the

kinetics of GF release,

GF interactions,

GF availability at the site of tissue damage

- presence (L-PRP) or not of neutrophils (P-PRP)
- neutrophils may exacerbate tissue damage through proinflammatory cytokines,

PRP-1 system

concentrated platelets (1.99× / blood)

diminished leukocytes (0.13×)

PRP-2 system

concentrated platelets (4.69×)

concentrated leukocytes (4.26×)

| | PRP-1 | PRP-2 | |
|---|---|---|---|
| PDGF (ng/mL) | 6.4 ± 0.5 | 22 ± 4.7 | P<0.05 |
| TGF-β (ng/mL) | 20 ± 12.9 | 89 ± 12.9 | P<0.05 |
| MMP-9 (ng/mL) | 40 ± 4.3 | 222 ± 32.9 | P<0.05 |
| IL-1β (pg/mL) | 0.31 ± 0.06 | 3.67 ± 1.2 | P<0.05 |

Sundman et al. 2011

## Growth factors and Platelet-Rich Plasma (PRP)

The speed and quality of myofiber regeneration is related to the kinetics of GF release,

GF interactions,

GF availability at the site of tissue damage

- presence (L-PRP) or not of neutrophils (P-PRP)
- neutrophils may exacerbate tissue damage through proinflammatory cytokines,

- what is the exact GF composition of PRP extracts ?

according to the preparation method,

the inter-, intra-individual variability …

# Conclusions

1) Muscle recovery after injury results from a

very sophisticated biological machinery that involves growth factors, cytokines, transcription factors and several intracellular pathways, in sequential cellular steps.

fine balance between positive (HGF, FGF, PDGF, IGF-1) and negative regulators (TGFβ).

2) The potential use of growth factors and cytokines extracted from PRPs is of potential interest but

- is PRP an ideal means for improving muscle healing ?
- are GF interesting for improving myofiber repair ?
- how to improve the expected effects of PRP ?

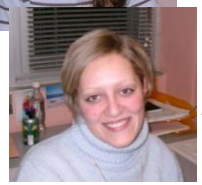
# the ideal balance between stimulatory and inhibitory factors

# conditions of extraction.

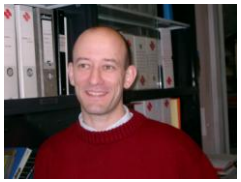
# *Team « Biomechanics-Muscle-Nutrition »*

*Nathalie Koulmann*

*Nadine Simler*



*Rachel Chapot*



*Sébastien Banzet*

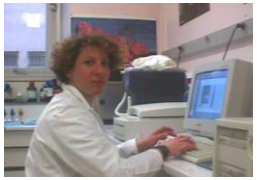
*Bernard Serrurier*

*Hervé Sanchez*

*Alexandra Malgoyre*

*Estelle Habouzit*

*Hélène Richard*



*Emmanuelle Fink*

*Olivier Birot*

Thank you for your attention …