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COMMENTARY

Ischemic Damage of the Flaps: New Treatments

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Every surgeon subjects the tissue of their patients to ischemic damage when performing a flap (pedunculated or microsurgical). The greater the ischemic damage, the more the body's repair mechanisms will be stressed and activated. If the damage exceeds the tissue resistance and reparative abilities of the organism, the flap will develop necrosis (completely or partially).

Many linked factors can occur in damaged flaps [1, 2] including venous stasis [3], insufficient blood supply, or the presence of hematomas, and all of these events contribute in different ways to ischemic damage [4].

Between 1970 and 1980, many studies were conducted on the survival of the flaps [4–7] to identify the elements that could induce necrosis [8].

In the following years, researchers focused on microcirculation and the flap peduncle and found that by increasing the blood flow [9–11], it was possible to improve the result [12].

The story became more interesting as we increased our understanding of the molecular aspects of the survival mechanisms of the flaps. Over the years, in fact, we have identified the molecular factors involved in response to ischemic damage and oxidative damage, the factors involved in ischemia-reperfusion injury, and the proteins and transcription factor protagonists of these phases. These findings are radically changing our approach to the treatment of ischemic insult; researchers and clinicians are now able to intervene before, during, and after these critical events to increase the overall number of cells that survive after an ischemic insult.

WHAT HAPPENS DURING ISCHEMIC DAMAGE?

When blood circulation is insufficient, the amount of oxygen in the tissues decreases dramatically. The cell's constant desire for adenosine triphosphate (ATP) is no longer fulfilled by the mitochondria, so the levels of adenosine monophosphate (AMP) increase. AMP is converted into adenosine, then into inosine, and then into hypoxanthine [13].

At the same time, the energy imbalance inside of the cell also leads to an imbalance of intracellular calcium with activation of a protease that converts xanthine-dehydrogenase to xanthine-oxidase. This event has a crucial role; while the "dehydrogenase" form uses nicotinamide-adenine-dinucleotide (NAD) as a hydrogen ion acceptor, the "oxidase" form uses oxygen directly (which is present in smaller quantities during ischemia). If the flow is not restored, the cell dies.

Proper restoration of oxygen intake (or its partial recovery) allows the cell to "breathe again"… and this causes further damage!

In fact, the presence of oxygen allows hypoxanthine oxidase to function properly, transforming hypoxanthine into uric acid and generating the superoxide ion $O2^{-}$.

Superoxide ion is a reactive oxygen species that under normal conditions is converted by superoxide dismutase (SOD) into hydrogen peroxide (H_2O_2). In these circumstances, however, the amount of H_2O_2 can increase with formation of large amounts of radical hydroxyl (OH^{-}) [14] in the presence of iron.

Other reactive oxygen species may also be formed by resuming activity of the respiratory chain in the mitochondria damaged by the previous ischemic insult.

Knowledge of these molecular mechanisms allows us to intervene and limit the damage. For example, we can limit the formation of free radicals by inhibiting xanthine oxidase. Mehdi Rasti Ardakani et al. have shown that the rate of necrosis of flaps is significantly reduced in dogs treated with

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a daily dosage of 50 mg/kg of allopurinol (which inhibits xanthine oxidase) [15].

In 2017, Peng-fu et al. showed that oxytocin improves the survival of flaps by increasing the activity of SOD, thereby increasing the ability of the cell to manage oxidative stress [16].

Beyond this, however, attempts have been made to use other molecules as growth factors and antioxidant agents, and the molecules of interest have become more and more numerous during recent years.

Recently, some researchers have focused on the anti-inflammatory and antioxidant roles of morroniside, an extract of the Cornus officinalis plant that supports vasal repair mechanisms.

A Chinese research group recently studied the use of morroniside on flaps in rats [17]. The team performed 9 cm ×3 cm McFarlane flaps in forty rats, and morroniside was injected intraperitoneally in twenty rats. The researchers observed a higher percentage of survival in the treated group ($p < 0.05$) as well as better demarcation of the necrotized area. This was accompanied by improved blood perfusion in the central area of the flaps, which was determined by laser-doppler and angiography and confirmed with histological analysis. The capacity of morroniside to stimulate angiogenesis was confirmed by the increase in the number of VEGF-positive cells in the treated group, and its anti-oxidant ability was manifested by an increase in SOD activity [17, 18].

Previous research has already demonstrated the role of morroniside in improving vascularization and reducing ischemia-revascularization damage, and now its role in the flaps has also been investigated [19, 20]. The study of pro-neoangiogenetic molecules with antioxidant effects has received more and more attention over time. This is not only limited to flap survival, but also includes some pathological conditions such as cerebral and myocardial infarction in which the ischemia occurs prior to ischemic-revascularization damage and can result in devastating outcomes for patients. Studies of molecules able to support ischemic conditions are often more numerous, especially in Asian countries, and we hope that these molecules, currently in the experimental phase, can soon be widely used in clinical practice.

DISCLOSURE STATEMENT

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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