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EDITORIAL

The Three "Musketairs" – Lasker Prize 2016 goes to the protagonists of hypoxia research

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Who does not know them? One bearded like a pirate, one knighted by the Queen, and one of noble spirit. United in the fight for truth and honor! No, this is not about Alexandre Dumas' characters Porthos, Athos, and Aramis, well-known from the famous novel *The Three Musketeers*.[1] This is about the most recent awardees of the Albert Lasker Basic Medical Research Award, the three protagonists of hypoxia research Gregg Semenza, Sir Peter Ratcliffe, and Bill Kaelin. The recent bestowal of the Lasker Prize is just another hallmark in a long list of recognitions of the major achievements by these three outstanding colleagues. What major victories in the battle against the unknowns in hypoxia research did our three heroes achieve?

Undoubtedly, Gregg Semenza initiated the hypoxia tale by cloning, together with his combatant Guang L Wang, the hypoxia-inducible factor. Following his initial description in 1992 of a unique hypoxia-inducible band in electrophoretic mobility shift assay (EMSA)[2], designated hypoxia-inducible factor (HIF), many tried to unravel the nature of this protein binding to the erythropoietin 3'-hypoxia response element. But it was not until 1995 that Wang and Semenza succeeded in identifying HIF as a heterodimer consisting of a known protein (HIF-1β or ARNT) and a novel hypoxia-inducible protein (HIF-1α).[3] Their cloning attack followed a classical but tedious strategy: purifying the activity from hundreds of liters of cell culture and using EMSA to trace the suspect. All the many other sophisticated strategies devised by competing groups basically failed. Nevertheless, the finding that HIF regulates not only erythropoietin but hundreds of other target genes[4,5] attracted the attention of many other kingdoms, which then entered the hypoxia battlefield, with "oncology" at the forefront. It quickly became clear that the crucial step in hypoxia-inducible gene expression is the oxygen-dependent destabilization of the HIFα subunit. But how oxygen interacted with HIFα remained a mystery well protected from the sorcerers of the invading kingdoms. Many mysterious molecular saboteurs were under suspicion, such as mitochondria, reactive oxygen species, redox state, general metabolism, and so on, but none of them could be arrested for HIFα destruction (reviewed by Wenger[6]).

This is when Sir Peter Ratcliffe and his men, including Patrick H Maxwell and Chris W Pugh, struck out for their first victory. By using a powerful weapon (antibodies against HIF-2α), still difficult to forge nowadays, they hunted down a tumor suppressor protein, known as "von Hippel-Lindau" (pVHL), guilty of oxygen- and iron-mediated HIFα demolition.[7] Other strategies were blunt swords in this battle, because antibodies

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against HIF-1α proved futile in studies using pVHL-deficient renal cancer cell lines, simply because many of these cell lines initially contained supramaximal toxic HIF-1α levels, which cancer selects against and instead selects for HIF-2α expression.[8] This seminal discovery of the E3 ligase pVHL, targeting HIFα for polyubiquitination and proteasomal degradation, finally provided the long-sought-for magic bullet that allowed the differentiation between hypoxic (nonmodified) and normoxic (modified) HIFα, because pVHL stably interacts with HIFα only under conditions compatible with the presence of an enzymatic activity that is oxygen- and iron-dependent.

Once the front lines were set, the events were overturning. The alliance between the mighty forces led by Bill Kaelin on one side, and with Sir Peter Ratcliffe and his men on the other side, quickly resolved the covalent modification of HIFα, which serves as recognition interface between HIFα and pVHL: oxygen derived from atmospheric air is used to hydroxylate two prolyl residues in the oxygen-dependent degradation domain of HIFα – a truly elegant and simple mechanism to combine oxygen sensing with signal transduction.[9,10] What was remaining was the identification of the responsible enzyme(s), but the resistance to reveal this final secret was weak. Sir Peter Ratcliffe struck out for his second and final victory by employing a heretofore unknown fairy army hidden only a few steps away from his headquarters. With the help of the simple genetics of these almost invisible creatures (known to the informed world as *Caenorhabditis elegans*), a new family of enzymes could be identified which use oxygen and 2-oxoglutarate as cosubstrates to hydroxylate HIFα subunits and to produce succinate by oxidative decarboxylation of 2-oxoglutarate in an iron- and reducing-agents-dependent process.[11]

During the following years, many scientists and companies were attracted by the shining lights of the treasures uncovered by Semenza, Ratcliffe, and Kaelin. Their findings fill libraries with more than 14,000 publications on HIF (and over 133,000 publications on hypoxia in general). Clinical trials are currently conducted, and it is likely that patients will soon profit from these amazing discoveries, a fact that was certainly also contributing to the decision to honor the Three "Musketairs" with the Lasker Prize.

The fandom is looking forward to the next chapters of the hypoxia saga to be written by our three heroes.

Disclosure

The authors report no conflicts of interest in this work.

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